

**Distribution of Patients in Subgroups and Reasons for Exclusion,  
All Treated Patients: Protocol AI420-037**

Subgroup/Reason	Number of Patients (%)					
	Gatifloxacin		Ceftriaxone		Total	
<b>Treated</b>	141	(100)	142	(100)	283	(100)
<b>Clinically Eligible</b>	136	(96)	140	(99)	276	(98)
<b>Clinically Ineligible</b>	5	(4)	2	(1)	7	(2)
<u>Reason Ineligible</u>						
No Evidence of Pneumonia on Pre-treatment X-ray	5	(100)	2	(100)	7	(100)
<b>Clinically Evaluable</b>	104	(74)	108	(76)	212	(75)
<b>Clinically Unevaluable</b>	37	(26)	34	(24)	71	(25)
<u>Reason Clinically Unevaluable</u>						
Inadequate Dosing	14	(38)	8	(53)	32	(45)
No Test of Cure Visit	7	(19)	6	(18)	13	(18)
Patient Clinically Ineligible	5	(14)	2	(6)	7	(10)
Test of Cure Visit Outside of "window"	4	(11)	-		4	(6)
Received Other Systemic Antibiotic	5	(14)	5	(15)	10	(14)
Received >1 dose of Systemic Antibiotic Pre-treatment	2	(5)	3	(9)	5	(7)
<b>Microbiologically Evaluable</b>	50	(35)	54	(38)	104	(37)
<b>Microbiologically Unevaluable</b>	91	(65)	88	(62)	179	(65)
<u>Reason Microbiologically Unevaluable</u>						
No Pathogen Documented	70	(77)	65	(74)	135	(75)
Clinically Unevaluable	14	(15)	15	(17)	29	(16)
Pathogen Is Resistant to one or more Study Drugs	7	(8)	8	(9)	15	(8)

(Reference: Vol 4, p 71)

Three patients did not receive study medication, one in the gatifloxacin arm (035-017) and two in the ceftriaxone arm (036-250, 056-086). These patients are removed from all further analyses. Patient 008-006 was initially treated with IV ceftriaxone but erroneously received oral gatifloxacin as step-down therapy; this patient is also removed from all subsequent analyses.

**Medical Officer Comment:**

FDA review of reasons for Clinically Ineligibility via examination of SAS transport data sets and CRF was generally in agreement with the applicant's table (see above). Review of the reasons for Clinically Unevaluability was also in agreement except for one patient. This patient received 7 days of gatifloxacin and died on the 7th day of COPD according to the investigator. This patient was listed as not having a test of cure visit(#37-00025). In a conservative analysis this patient would have been treated as a clinical failure.

Review of the reasons for Microbiologically Unevaluability via examination of SAS transport data sets and CRF was generally in agreement with the applicant's table (see above).

In general, the two treatment groups were balanced with regard to number of patients excluded from various analysis cohorts. Two percent of patients randomized were ineligible, 25% were clinically unevaluable, and 63% were microbiologically unevaluable for analysis according to the protocol established criteria.

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:** Gatifloxacin 400 mg IV, Lot numbers C97201, C97318, C97319; Gatifloxacin tablets, 400 mg PO, Lot numbers N97076, N97078; matching placebo tablets, Lot numbers N97092, N97116. Tablets were supplied in blister cards.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:** Ceftriaxone 1 gm IV, Lot numbers 5900, 0938, 5921, 0946, 5878; Erythromycin 500 mg IV, Lot number 30803Z7; Clarithromycin tablets 500 mg PO, Lot numbers N97125, N97185, N97135; matching placebo tablets, Lot numbers N97071, N97132. Tablets were supplied in blister cards.

**8.1.2.1.4 DURATION OF TREATMENT:** Gatifloxacin QD (IV to PO or IV only) x 7 to 14 days; ceftriaxone QD with or without erythromycin Q6H (IV to clarithromycin BID PO or IV only) x 7 to 14 days.

All gatifloxacin patients received IV gatifloxacin at a dose of 400 mg (Table 9.1.1). Approximately two-thirds of ceftriaxone patients received one gram IV daily; the remainder received two grams IV daily. More than one-third of ceftriaxone-treated patients received concomitant IV erythromycin every six hours, the dose of which was 0.5 grams in all but five patients.

**APPEARS THIS WAY  
ON ORIGINAL**

**IV Dosing Regimen, All Treated Patients  
Protocol AI420-037**

Gatifloxacin/Ceftriaxone Dose <sup>a</sup>	Erythromycin Dose <sup>b</sup>	Number of Patients (%)	
Gatifloxacin 400 mg	-	141	(100)
Ceftriaxone 1 or 2 gm <sup>c</sup>	-	142	(100)
1 gm	Any	96	(68)
	None	56	(58)
	0.5 gm	37	(39)
	1 gm	3	(3)
2 gm	Any	45	(32)
	None	29	(64)
	0.5 gm	14	(31)
	1 gm	2	(4)

<sup>a</sup> Once daily.

<sup>b</sup> Every 6 hours if prescribed.

<sup>c</sup> One patient randomized to ceftriaxone received a single 500 mg dose of erythromycin and was discontinued from the study because of nausea (045-031). This patient is not represented in the table. (Reference: Vol. 4, p. 87)

In both treatment groups, 85% of patients received IV followed by oral therapy and 15% received IV therapy only. Among patients who stepped down to oral therapy, the median duration of IV therapy in both treatment groups was three days. Seventy-eight (78) percent of patients received 7-14 days of therapy. Twenty-eight patients received four or fewer days of IV therapy only (12 gatifloxacin, 16 ceftriaxone). Twelve of these patients discontinued prematurely due to an AE (4 gatifloxacin, 8 ceftriaxone), six patients withdrew consent (2 gatifloxacin, 4 ceftriaxone) and two patients developed an intercurrent illness (1 gatifloxacin, 1 ceftriaxone). In the gatifloxacin group, two additional patients died, two did not respond to therapy, and one was stepped-down to oral therapy but did not return for follow-up. In the ceftriaxone group, one additional patient was transferred to another hospital, one had a resistant pre-treatment pathogen and one was discontinued because of having possibly missed a dose of ceftriaxone. Six patients (4 gatifloxacin, 2 ceftriaxone) received fourteen days worth of therapy over longer than fourteen days (5 over 15 days, 1 over 18 days). Sixteen patients (8 gatifloxacin, 8 ceftriaxone) actually received more than fourteen days worth of therapy.

**APPEARS THIS WAY  
ON ORIGINAL**

**Study Medication Usage, All Treated Patients  
Protocol AI420-037**

	Number of Patients (%)					
	Gatifloxacin N = 141		Ceftriaxone N = 142		Total N = 283	
<u>Duration (Days)</u>						
<u>IV+ PO</u>	120	(85)	121	(85)	241	(85)
3 - 4	4	(3)	1	(<1)	5	(2)
7 - 9	14	(12)	13	(11)	27	(11)
10	28	(23)	28	(23)	56	(23)
11 - 13	31	(26)	29	(24)	60	(25)
14	31	(26)	40	(33)	71	(29)
15 - 18	12	(10)	10	(8)	22	(9)
<u>IV Route Only</u>	21	(15)	21	(15)	42	(15)
1 - 4	12	(57)	16	(76)	28	(67)
5 - 6	5	(24)	2	(10)	7	(17)
7 - 14	4	(19)	3	(14)	7	(17)

(Reference: vol 4, pp 87-89)

**Medical Officer Comment:**

*In general, the exposure to study therapy was similar between the two treatment groups.  
(Outcome analysis by dose is commented on in the efficacy section below).*

**APPEARS THIS WAY  
ON ORIGINAL**

**8.1.2.1.5 CRITERIA FOR EVALUATION:**

Clinical and bacteriologic responses were determined from data at the Test of Cure Visit scheduled between Day +7 to Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit between Day +5 to Day +28 inclusive was acceptable. Treatment Failures could be assessed at any time during the treatment and follow-up periods, but patients had to receive a minimum of three days' study drug therapy.

**Study Procedures: Protocol A1420-037**

Procedure	Pre-treatment (within 48 hrs prior to dosing)	During Treatment (Days 2 to 4) <sup>a</sup>	End of Treatment (Days +1 to +3) <sup>b</sup>	Post- Treatment (Days +7 to +14) <sup>a</sup>	Final Follow-up (Days +21 to +28) <sup>c</sup>
Informed Consent	X	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-
Medical History	X	-	-	-	-
Physical Exam	X	X <sup>d,e</sup>	-	X	X <sup>d,f</sup>
Vital Signs <sup>g</sup>	X	X <sup>e</sup>	-	X	-
Clinical Symptoms	X	X <sup>e</sup>	X	X	X
Clinical Signs	X	X <sup>e</sup>	-	X	X <sup>f</sup>
O <sub>2</sub> Saturation or ABG <sup>h</sup>	X	X <sup>i</sup>	-	-	-
Blood Cultures	X	X <sup>i,j</sup>	-	X <sup>i,j</sup>	X <sup>i,j</sup>
Respiratory Specimen Evaluation	X <sup>k</sup>	X <sup>k</sup>	-	X <sup>k</sup>	X <sup>k</sup>
Chest X-Ray	X	X <sup>i</sup>	-	X	X <sup>f</sup>
Laboratory Tests	X	X <sup>l,m,n</sup>	-	X <sup>m</sup>	-
Serology Test	X <sup>o</sup>	-	-	X	X
Oropharyngeal Swabs <sup>p</sup>	X	-	-	-	-
Pregnancy Test	X	-	-	X	-
Assess Adverse Events	-	X	X	X	X
Assess Study Medication Use	-	X	X	X	-

<sup>a</sup> Patients discontinuing study prematurely will have post-treatment procedures performed prior to non-study antibiotic administration.

<sup>b</sup> Telephone contact. Immediate office visit and post-treatment procedures if the patient is not clinically improved.

<sup>c</sup> An office visit will be required during this time interval in all patients.

<sup>d</sup> Chest exam only.

<sup>e</sup> Repeat daily while hospitalized.

<sup>f</sup> If evidence of relapse.

<sup>g</sup> Blood pressure, pulse, respiratory rate, temperature.

<sup>h</sup> Oxygen saturation by pulse oximeter on room air or arterial blood gas on room air.

<sup>i</sup> If clinically indicated.

<sup>j</sup> If previous blood culture is positive.

<sup>k</sup> Macroscopic evaluation, Gram stain, culture/susceptibility testing if specimen obtained.

<sup>l</sup> Repeat every 3-5 days while hospitalized.

<sup>m</sup> Must be done. All abnormal laboratory test results should be repeated until they return to pre-treatment levels or are deemed clinically insignificant by the investigator.

<sup>n</sup> Two blood samples (i.e., trough and peak) may be drawn for PK assessment on Day 2, or thereafter for those consenting patients who remain on IV therapy.

<sup>o</sup> Including *Legionella* urinary antigen.

<sup>p</sup> Two swabs, 1 for PCR (*M. pneumoniae*, *C. pneumoniae*, *Legionella* sp.) and *M. pneumoniae* culture, 1 for *C. pneumoniae* culture. (Reference, Vol 4, p. 40)

Indication: Community Acquired Pneumonia (Study 037)

Revision Date: 22-Nov-99

**Medical Officer Comment:**

*It is of interest to note that the applicant changed the test of cure window from +7 to +14 days to +5 to +28 days inclusive. This was done in an analysis plan submitted to the FDA prior to the Database Unblinding. FDA and the applicant discussed this change, specifically the concern by FDA that the expanded window may complicate the analysis of relapse and failure. FDA noted that it would be important to indicate how many patients did not come back for follow-up at the later visit (+21 to +28 days).*

*The majority of patients were evaluated for Test of Cure (TOC) during the +7 to +14 day window. The range was +6 to +22 days. There were 22 patients in the gatifloxacin group and 14 in the ceftriaxone group whose TOC evaluation fell outside the +7 to +14 day window. Only 4 patients, all in the gatifloxacin group, were seen in the +21 to +28 day window as the Test of Cure (#36-00252, # 36-00443, # 40-00353, # 52-00203). All of these patients were considered cures. All of these patients were showing signs of improvement during study and had late follow-up clinically and radiographically. All CXRs either improved or resolved, and no further antibiotics were administered to these patients. It is acceptable to include these as cured in the analysis.*

*The sponsor supplied additional information regarding the patients who returned for the +21 to +28 day follow-up visit.*

*"One hundred eighty-group (184) of the clinically evaluable subjects were cured. Of these 129 had a Day +21 to +28 follow-up visit and 55 did not. Of these 55 subjects, 12 had NO late follow-up and 43 had a follow-up visit after day +14 but outside of the day +21 to +28 window."*

*FDA review of this data revealed that 15 patients did not have late follow-up after Day +14. Eight were in the gatifloxacin group and 7 were in the ceftriaxone group. If these were counted as Relapses this would make the overall number of relapses 9 % (9/104) in the gatifloxacin group and 7% (8/108) in the ceftriaxone group. These are small numbers and the rates are similar between groups. When an overall success/failure outcome is calculated, including failures and relapses, the comparative outcomes between the groups remains unchanged. (Please refer efficacy evaluation for further details).*

**8.1.2.1.6 OUTCOME EVALUATION:****Clinical Evaluation:**

Each patient was assigned a clinical response of Cured, Failure, or Unable to Determine.

**Medical Officer Comment:** *FDA reviewed each of these assignments for outcome. The results of each review are listed in a Medical Officer Comment following the protocol definition for each outcome.*

**CURED:**

- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required and chest x-ray abnormalities were improved or had not progressed; OR
- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and no during or post-treatment chest x-ray was performed (These patients were not included in the evaluable subset).

*Medical Officer Comment: For all of the "cured" patients who were considered evaluable, signs and symptoms were reviewed via JMP data base for the Test of Cure Day. For the majority of patients that day was within +7 to +14 days after the end of therapy. The following distribution was seen in symptom response:*

*FDA Evaluation of Cured by Clinical Status of Signs and Symptoms*

Symptom Response	Number of Symptoms	Number of Symptoms Related to CAP	Number of Cured Patients with CAP Symptoms
Resolved	1386	935	182
Improved	226	181	90
Same	13	11	10
Worse	6	4	3
Unknown	29	11	10
New	8	0	0

*\*note that the patient category is not mutually exclusive as the patients had two or more signs and symptoms evaluated.*

*For the majority of symptoms recorded, the outcome evaluation was Resolved. Further review of the total symptom base revealed a subset of symptoms that defined CAP. The total number of patients with one or more CAP symptom reported to have resolved was 182 or 86% of the clinically evaluable population. These symptoms were evenly divided between the treatment groups (ceftriaxone group 48%, gatifloxacin group 52%).*

*As per the definition of cure, all signs and symptoms were to have resolved or improved to such a level that no further antibiotics were needed. As noted in the table, several patients had CAP symptoms that remained the same, worsened, or were of unknown resolution. Because the TOC cure window was widened to include the follow-up visit at +21 to +28 days; however, review of these patients revealed no further worsening. In addition, other signs and symptoms in the same patient improved or resolved and the CXRs were improved or resolved. Of the 3 patients who had symptoms recorded to have worsened, all were on the gatifloxacin arm. One patient had improvement or resolution of other symptoms, improvement on chest x-ray. The symptom, rales was graded as having worsened in the SAS transport file, but new on the CRF. The patient stated that he was told he had rales from time to time due to his asbestosis (#25-0015). The second patient had resolution and improvement of symptoms, except for malaise which was graded as worsened, but was related to underlying disease and not pneumonia (#33-*

00176). The last patient had improved CXR and improved or resolved signs and symptoms. On follow-up patient was diagnosed as having an exacerbation of COPD and was admitted to the hospital. Again the CXR did not show evidence of active pulmonary disease(#39-00236). This patient was not considered a relapse but a cure. Review of the CRF by the FDA reviewer agrees in general with counting these as cures.

Regarding the issue of Cure representing strictly the Resolved signs and symptoms versus resolved and improved, the original study design allowed for evaluation of patients at the +7 to +14 day window and again at the +21 to +28 day window. This would allow any patient with improved symptoms the opportunity to further resolve or continue to worsen, thus representing a relapse. When the applicant widened the window this made the definition of cure more difficult. As it turned out, most of the patients reported symptoms that resolved and most of the evaluation days were in the earlier window. Therefore, upon review of patients who had symptoms that improved as opposed to resolved, further investigation was undertaken, via examination of CRF to ensure that these patients did not relapse at a later date. Only one of the patients listed with improved symptoms at TOC date went on to become a relapse (# 11-00421).

Finally, the assignment of cure that was used by the applicant was the one assigned by the applicant and not necessarily that checked off by the clinician at the time of final evaluation. There were only a small number of discrepancies between these assignments. FDA review of these changes was in agreement with the applicant review. This was mostly due to additional data which was available at the time of the applicant review. There were 13 reassignments to failure by the applicant, 5 in the gatifloxacin group and 8 in the ceftriaxone group.

Given the review of the definition of cure and the criteria used in this study, the FDA is satisfied with and accepts the applicant's assignment of cure.

#### FAILURE:

One or more of the following:

- Signs and symptoms relevant to the original infection persisted or progressed after at least 3 days of therapy;
- New pulmonary or extrapulmonary clinical findings consistent with pneumonia developed;
- Radiographic abnormalities progressed;
- Additional antimicrobial therapy was needed for treatment of the pneumonia under study;
- Patient died and death was due to pneumonia.

Two patients in the gatifloxacin group were judged by the applicant to be failures due to death from pneumonia. Patient 011-368 was an 82-year-old female with pneumonia complicated by empyema due to *S. pneumoniae* (pre-treatment sputum and pleural fluid culture-positive). The patient was intubated on Day 1 and required 100% FiO<sub>2</sub>, along with dopamine. She died, still intubated in the ICU on Day 6 of IV therapy, in the setting of acutely diagnosed myelomonocytic leukemia. Patient 053-298 was a 92-year-old

female with severe (i.e., hypoxia, bilateral infiltrates), bacteremic *H. influenzae* pneumonia. Her history was notable for pulmonary fibrosis, diabetes mellitus and chronic renal insufficiency. She expired on her seventh day of IV therapy. In hindsight, neither of these patients were appropriate for this study, each having violated exclusion criteria (empyema/leukemia and renal insufficiency, respectively).

Eight of the treatment failures in the gatifloxacin group, and nine in the ceftriaxone group, were in patients who had one or more pre-treatment pathogen identified. *S. pneumoniae* was by far the most commonly isolated pathogen, occurring in 10 of these 17 patients (6 gatifloxacin, 4 ceftriaxone). While none of the gatifloxacin *S. pneumoniae* treatment failures were bacteremic, two of the ceftriaxone failures (011-366, 013-385) had documented pre-treatment *S. pneumoniae* bacteremia.

Two of the six *S. pneumoniae* failures in the gatifloxacin group had a complicated course: patient 039-235 had a respiratory arrest on Day 5 due to a mucous plug and was emergently intubated; and patient 011-368 had pneumococcal empyema and acute leukemia (described above). The remaining four patients were declared failures despite radiographic improvement; three (011-367, 039-069, 078-337) patients were given post-treatment antibiotics for "bronchitis" or "URI" and one patient (043-341) was not given post-treatment antibiotics. In contrast, three of the ceftriaxone *S. pneumoniae* failures had progression of radiographic abnormalities including the two patients with *S. pneumoniae* bacteremia: patient 011-366 had progression of radiographic abnormalities plus new rales; and patient 013-385 had progression of radiographic abnormalities and received post-treatment IV antibiotics. In addition, patient 013-075 had progression of radiographic abnormalities, along with worsened signs and symptoms and was given post-treatment IV antibiotics. Lastly, patient 001-003 was given post-treatment antibiotics for "bronchitis".

**Reason Clinical Response is Failure,  
Clinically Evaluable Patients  
Protocol A1420-037**

Frequency/Reason	Number of Patients (%)					
	Gatifloxacin N = 104		Ceftriaxone N = 108		Total N = 212	
Number of Failures	12	(12)	16	(15)	28	(13)
Persistence/Worsening/New Primary Signs/Symptoms	9	(75)	11	(69)	20	(71)
Worsening of Radiographic Abnormalities	1	(8)	5	(31)	6	(21)
Death Due to Pneumonia	2	(7)	-	-	2	(7)

(Reference: vol 4, p 104)

**Medical Officer Comment:**

FDA review of the CRFs of the above cases is in agreement with the applicant's assignment of failure. It should be noted that 7/12 gatifloxacin patients and 10 of 16

*ceftriaxone patients were subsequently treated with antibiotics. Neither of the gatifloxacin deaths were noted to have received other antibiotics.*

#### UNABLE TO DETERMINE:

Clinical response was termed Unable to Determine (UTD) for patients in whom a post-treatment evaluation of clinical signs and symptoms was not obtained, or in whom another systemic antibiotic with documented activity against the isolated pathogen(s) for an infection other than pneumonia, was administered prior to evaluation.

Forty-six patients had a clinical response of unable to determine (Table 10.2.1.2). The most common reason was discontinuation of therapy because of an AE, which accounted for seven patients in each treatment arm. Four of the AEs in the gatifloxacin arm and five in the ceftriaxone arm were considered to be related to study therapy. The miscellaneous reasons for the clinical response of unable to determine in the gatifloxacin group were death in both patients (037-025, 071-195). In the ceftriaxone group, the miscellaneous reasons were early discontinuation because of a resistant pathogen, transfer to another hospital, and discontinuation due to possible missed doses of ceftriaxone (004-157, 035-019 and 048-116, respectively).

#### Reason Clinical Response is Unable to Determine, Clinically Eligible Patients Protocol AI420-037

Reason	Number of Patients		
	Gatifloxacin N = 136	Ceftriaxone N = 140	Total N = 276
Number of Responses Unable to Determine	24	22	46
Inadequate Follow-up	5	1	6
Other Systemic Antibiotic Given for an Infection Other Than Pneumonia	4	2	6
Other Reasons:	15	19	34
SAE Discontinuation due to AE or	7	7	14
Withdrew Consent	3	6	9
Intercurrent Illness	2	2	4
Concomitant Antibiotics	1	1	2
Miscellaneous	2	3	5

Reference: vol 4, p. 119)

#### Medical Officer Comment:

*FDA review of SAS files and CRFs verified the above table. Patients who were listed as unable to determine outcome and had an adverse event listed as the reason, received generally less than 5 doses of medication and were withdrawn from the study. The number of patients ranked as unable to determine is similar between the two treatment*

groups. Calculation of the efficacy rates would include these patients in the denominator for the rate calculation in the Clinically Eligible analysis and these patients would be excluded from the Clinically Evaluable analysis.

#### 8.1.2.1.7 MICROBIOLOGICAL EVALUATION:

Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted or Unable to Determine according to definitions in the protocol. Typical bacterial pathogens such as *S. pneumoniae* were microbiologically evaluable for response only if susceptible to the study drugs (i.e., gatifloxacin, ceftriaxone and clarithromycin). Atypical bacterial pathogens, regardless of diagnostic method, were microbiologically evaluable for response.

##### *Medical Officer Comment:*

Microbiological Response was based upon clinical response of the patient who had a documented pretreatment pathogen. Thus, the response category of Cure is a clinical one, but when used in the expression Bacteriologic Eradication may connote the impression that the pathogen was demonstrated to be microbiologically eradicated. This leads to confusion when expressing the result for serologically diagnosed atypical pathogens, especially where the documentation of a single high titer made the diagnosis. Therefore, this reviewer recommends the results be discussed as a clinical response based upon a microbiologic diagnosis at entry.

The impact of this syntax will be discussed in the analysis section, and will include critique of the shorthand expression "Bacteriologic" eradication rate, where, especially for the atypical pathogens it is very misleading.

#### 8.1.2.1.8 STATISTICAL METHODS:

*Data Sets* -- There were four groups of interest:

- All Treated Patients: All patients who received at least one dose of study drug.
- Clinically Eligible Patients: All treated patients with a diagnosis of community-acquired pneumonia at entry.
- Clinically Evaluable Patients: All Eligible Patients who met the minimum dosing requirement of at least 5 days, (at least 3 days for treatment failures), had an end-of-treatment (in the case of failure) or post-treatment (Test-of-Cure) assessment with a chest x-ray in the interval Day +7 to Day +14, and did not receive a systemic antibacterial agent with documented activity against the causative pathogen between the time of the pre-treatment visit and the post-treatment assessment unless to treat a clinical failure.
- Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had a bacterial pathogen susceptible to both study drugs isolated from a pre-treatment sputum and/or blood culture, or an atypical pathogen diagnosed by culture, PCR, and/or serology; a sputum Gram stain performed for patients still producing sputum at the Test of Cure Visit, and a sputum culture performed for patients still producing sputum at the Test of Cure Visit if the sample was of good quality (i.e., >25 PMN and <10 epithelial cells/low power field).

**Efficacy Analyses** - The primary efficacy assessment was the clinical response taken at the Test of Cure Visit in the Clinically Evaluable group. Ninety-five percent confidence intervals for the difference in response rates were constructed using an exact method. Intervals were also constructed for the clinical response taken at the Test of Cure Visit in Clinically Eligible Patients and in All Treated Patients. Additional secondary efficacy analyses included clinical cure rate by prognostic factor and by severity of pneumonia for Clinically Evaluable Patients, as well as cure rate and eradication rate by pathogen for Microbiologically Evaluable Patients.

Based on an estimated 80% clinical cure rate for patients with community-acquired pneumonia treated with ceftriaxone, 150 evaluable patients per arm would yield a 90% power to claim the cure rate for the gatifloxacin arm is at most 15% less than the rate for the ceftriaxone arm ( $\alpha = 0.05$ , two-sided). Assuming this cure rate, and an 80% evaluability rate, the necessary sample size was calculated to be 376 patients, 188 patients per treatment arm. The accrual was stopped after 287 patients had been randomized because it was felt that the objectives of the study had been met.

*Medical Officer Comment: The primary reason for stopping the study early was to complete the data base for the submission of the NDA. The applicant maintained the blinding on the database until this decision was made. This decision is acceptable to the FDA. Of note is the potential for wider confidence intervals given the smaller number of patients accrued.*

*The All Treated and Eligible subsets would more closely represent the "intent-to-treat" population, while the Evaluable group represented the "per-protocol" analysis. The Microbiologically Evaluable subset represents a highly select group of patients who were evaluable and had a pathogen isolated from the sputum at study entry. All of these analysis will be considered by the FDA.*

**Safety Analyses** – All patients who received at least one dose of study drug were evaluated for safety. Safety data was collected between the first day of study drug therapy and 30 days after the last day of such treatment. Variables included deaths, adverse clinical events, serious adverse clinical events, discontinuation of study therapy, local IV intolerance, abnormal laboratory results, and pregnancy. All safety data were summarized with descriptive statistics and tabulated.

#### 8.1.2.2 EFFICACY RESULTS:

##### 8.1.2.2.1 Clinical Efficacy:

Two-hundred eighty three patients were treated with study drug (141 gatifloxacin, 142 ceftriaxone). Of the ceftriaxone-treated patients, 68% received one gm IV once daily and 32% received two gm IV once daily. Thirty-nine percent of ceftriaxone-treated patients received concomitant IV erythromycin. In both treatment groups, 85% of patients received IV followed by oral therapy; 15% received IV therapy only.

Among Clinically Evaluable Patients (N=212), the cure rates for gatifloxacin- and ceftriaxone-treated patients were 88% and 85%, respectively (95% C.I. -7.6%, 15.3%).

Equivalence was also demonstrated in Clinically Eligible Patients (74% gatifloxacin, 71% ceftriaxone; 95% C.I. -8.5%, 15.0%) and All Treated Patients (73% gatifloxacin, 70% ceftriaxone; 95% C.I. -8.4%, 14.8%). In Clinically Evaluable Patients with mild to moderate pneumonia, the cure rate in the gatifloxacin arm was 97% versus 88% in the ceftriaxone arm. In Clinically Evaluable Patients with severe pneumonia, the cure rate in the gatifloxacin arm was 85% versus 84% in the ceftriaxone arm.

#### Applicant Clinical Efficacy Analysis

Subgroup	Gatifloxacin	Ceftriaxone	Confidence Interval
All Treated Patients (N=283)	73% (102/141)	70% (103/142)	-8.4%, 14.8%
Eligible Patients	74% (100/136)	71% (99/140)	-8.5%, 15.0%
Evaluable Patients	88% (92/104)	85% (92/108)	-7.6%, 15.3%

*Medical Officer Comment: In general the FDA was able to verify the applicant's assessment as described above. However, additional sensitivity analyses were performed by the FDA. One of most conservative analysis counted the losses to follow-up as failures in the gatifloxacin group and successes in the ceftriaxone group. The confidence intervals were somewhat wider with this analysis -17%, -2.9%. These confidence intervals are wider due to the large amount of missing data in this study. The results of this conservative analysis would indicate that the results are not robust enough for this type of conservative analysis. A more clinically interesting analysis is that of global failure, where patients who failed at the "test of cure" visit or relapsed or had a new respiratory tract infection were counted as failures. The confidence interval for this analysis in the evaluable subset was -7.1%, 14.2%, very similar to the Clinically Evaluable patient response.*

*Subsequent analyses were undertaken because the patients could be treated with intravenous ceftriaxone therapy at the discretion of the attending physician, which is not active against atypical pathogens, and these patients could be additionally covered with erythromycin. The double-blind was maintained in this case as the ceftriaxone patients received erythromycin and the gatifloxacin patients received placebo erythromycin, as administered by the hospital pharmacist. The analyses of most interest tested the hypothesis that patients who were selected to receive erythromycin had a more severe case of pneumonia. Patients on either treatment arm were given erythromycin or placebo, in the case of gatifloxacin. The analysis is presented in the table below.*

#### Clinical Cure Rate by Erythromycin

Data Subset	Assigned Erythromycin	Gatifloxacin	Ceftriaxone
All treated patients	Yes	67%	59%
	No	76%	78%
Evaluable patients	Yes	93%	82%
	No	86%	87%

*FDA table derived from SAS datasets.*

*From this breakdown it appears that for patients who were judged to need erythromycin by their physicians, gatifloxacin plus placebo does better than ceftriaxone*

(clarithromycin) plus erythromycin. For subjects who were thought not to need erythromycin, ceftriaxone and gatifloxacin have similar clinical cure rates.

Finally, it is of interest to note that the failures are on IV longer than cures or unable to determine. Mean IV duration for cures is 3.7 days, for failures is 5.0 days, and for unable to determine is 3.0 days. Also, patients assigned to low ceftriaxone dose are on IV for similar number of days as those assigned to high dose.

The above analyses supports the efficacy of gatifloxacin for the treatment of community acquired pneumonia, including hospitalized patients.

#### 8.1.2.2.2 MICROBIOLOGICAL EFFICACY:

##### **Clinical Outcome for Microbiologically Documented Infections:**

More than half (52%) of all patients had one or more pre-treatment pathogen. Of the 224 pathogens, 187 (83%) were typical pathogens and 37 (17%) were atypical pathogens. All but one of the typical pathogens were susceptible to gatifloxacin; 24 were resistant to clarithromycin and/or ceftriaxone by NCCLS guidelines. Excluding patients with a clinical response of unable to determine, the clinical cure rate among Clinically Eligible Patients with clarithromycin and/or ceftriaxone-resistant pathogens was 100% (7/7) in the gatifloxacin arm and 75% (12/16) in the ceftriaxone arm.

Among Microbiologically Evaluable Patients (N = 104), a clinical response of Cured was obtained in 100% of gatifloxacin-treated patients with pre-treatment *M. catarrhalis*, *S. aureus*, *L. pneumophila*, *M. pneumoniae* and *C. pneumoniae*. Cure rates were notably higher in gatifloxacin Microbiologically Evaluable Patients with pre-treatment *M. catarrhalis* (100% vs. 75%), *L. pneumophila* (100% vs. 75%), *C. pneumoniae* (100% vs. 80%) and *S. aureus* (100% vs. 93%). One gatifloxacin patient with pre-treatment *H. influenzae* failed therapy and one ceftriaxone patient with pre-treatment *H. influenzae* was a clinical cure who relapsed.

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**Clinical Cure Rate by Pathogen,  
Microbiologically Evaluable Patients  
Protocol AI420-037**

Pathogen <sup>a</sup> / Subtype	Number Cured/Number Isolated or Documented (%)					
	Gatifloxacin N = 74		Ceftriaxone N = 80		Total N = 154	
<i>H. influenzae</i>	7/8	(88)	10/10	(100)	17/18	(94)
β-Lactamase +	0/1	(0)	2/2	(100)	2/3	(67)
β-Lactamase -	7/7	(100)	7/7	(100)	14/14	(100)
β-Lactamase Unknown	-		1/1	(100)	1/1	(100)
<i>S. pneumoniae</i>	16/22	(73)	18/21	(86)	34/43	(79)
Penicillin Susceptible	7/10	(70)	13/14	(93)	20/24	(83)
Penicillin Intermediate	2/3	(67)	2/3	(67)	4/6	(67)
Penicillin Resistant	1/1	(100)	-		1/1	(100)
Penicillin Susceptibility Unknown <sup>b</sup>	6/8	(75)	3/4	(75)	9/12	(75)
<i>S. aureus</i>	7/7	(100)	13/14	(93)	20/21	(95)
Methicillin Susceptible	7/7	(100)	13/14	(93)	20/21	(95)
<i>M. catarrhalis</i>	3/3	(100)	6/8	(75)	9/11	(82)
β-Lactamase +	2/2	(100)	5/7	(71)	7/9	(78)
β-Lactamase -	-		1/1	(100)	1/1	(100)
β-Lactamase Unknown	1/1	(100)	-		1/1	(100)
<i>H. parainfluenzae</i>	1/2	(50)	2/2	(100)	3/4	(75)
β-Lactamase -	1/2	(50)	2/2	(100)	3/4	(75)
<i>S. milleri</i>	3/3	(100)	-		3/3	(100)
Other Gram-positive <sup>c</sup>	8/10	(80)	5/5	(100)	13/15	(87)
Other Gram-negative <sup>d</sup>	4/4	(100)	6/7	(86)	10/11	(91)
<i>M. pneumoniae</i>	7/7	(100)	4/4	(100)	11/11	(100)
<i>L. pneumophila</i>	3/3	(100)	3/4	(75)	6/7	(86)
<i>C. pneumoniae</i>	5/5	(100)	4/5	(80)	9/10	(90)
<b>TOTAL</b>	<b>64/74</b>	<b>(86)</b>	<b>71/80</b>	<b>(89)</b>	<b>135/154</b>	<b>(88)</b>

<sup>a</sup> A patient may have more than one pathogen isolated pre-treatment.

<sup>b</sup> See Appendix-1D for those penicillin susceptibilities erroneously omitted from the database.

<sup>c</sup> Gram-positive pathogens isolated from <5 patients included [(x/y) = gatifloxacin/ceftriaxone]: *S. pyogenes* (2/0), alpha-hemolytic streptococcus (1/1), *S. viridans* (0/1), gamma-hemolytic streptococcus (1/0), *S. canis* (1/0), *S. agalactiae* (1/0), *S. sanguis* (0/2), *S. epidermidis* (3/0), *S. hominis* (1/1).

<sup>d</sup> Gram-negative pathogens isolated from <5 patients [as above]: *P. aeruginosa* (1/1), *K. pneumoniae* (1/0), *Haemophilus* sp. (1/1), *H. parahaemolyticus* (0/1), *Neisseria* sp. (1/2), *A. baumannii* (0/2).

(Reference: Vol. 4, p. 112)

**Medical Officer Comment:**

FDA review of the data base provided by the applicant is in agreement. It should be noted that patients may have more than one pathogen documented at baseline and the

above table applies clinical outcomes to each pathogen without designating which may be the putative agent causing the CAP.

*In addition this outcome measure subsets the clinically evaluable patients into a group having a microbiologic diagnosis (culture or serology) at baseline, with CURE being defined clinically. Thus, the oddity of stating that the Atypical Pathogens were eradicated in a microbiologically evaluable patient. Further analyses should be applied to some of these pathogens (see discussion of atypical pathogens below).*

*There was only one S. pneumoniae penicillin resistant isolate documented in this study which was considered a clinical cure in the gatifloxacin arm. Evaluation for this pathogen will be considered in the overall summary of CAP, where the opportunity to review additional isolates from other studies will be viewed.*

*For the major pathogens, S. pneumonia and H. influenza, there were sufficient numbers of patients with clinical isolates at baseline. Clinical outcomes for these pathogens were similar between treatment arms, although the gatifloxacin group had lower rates. M. catarrhalis infections represented less than 10% of microbiologically documented infections. Three such infections were treated in the gatifloxacin arm and all three were considered clinical cures.*

Ten of the 17 failures among Clinically Evaluable Patients with one or more pre-treatment pathogen identified had pre-treatment *S. pneumoniae* (gatifloxacin-6, ceftriaxone-4). However, two of the ceftriaxone failures were bacteremic pre-treatment, whereas the two bacteremic patients in the gatifloxacin group were cured. In addition, two PCN-intermediate *S. pneumoniae* isolates associated with ceftriaxone-failure displayed intermediate susceptibility to ceftriaxone as well. Finally, four of the six gatifloxacin *S. pneumoniae* treatment-failures had documented chest x-ray improvement or resolution at the Test of Cure Visit and were given antibiotics for bronchitis or URI. In contrast, three of the four ceftriaxone *S. pneumoniae* treatment-failures had documented worsening of radiographic findings, including the two bacteremic patients.

For many of the key respiratory pathogens among Microbiologically Evaluable Patients, "bacteriologic" eradication rates were higher in the gatifloxacin arm. Most notably were *M. catarrhalis* (100% vs. 75%), *L. pneumophila* (100% vs. 75%), *C. pneumoniae* (100% vs. 80%) and *S. aureus* (100% vs. 93%). The eradication rate for *M. pneumoniae* in both groups was 100%. Two pathogens were documented to persist at the Test of Cure Visit in each group and none of these persistent isolates displayed altered susceptibilities.

**Medical Officer Comment:**

*It is of interest to note that the eradication rate which is quoted by the applicant above is comprised of patients with documented eradication (positive culture followed by a negative culture, in the case of culture proven cases) or presumed eradicated (microbiologically evaluable without a follow-up culture). The majority of these responses "eradicated" were presumed eradication. The types of response were relatively similar between treatment arms. It is important to understand the use of the*

terms bacteriologic eradication rates, and that in this model it does not have the same stringency that it would in an animal model where confirmation of bacteriologic cure would have a much higher proportion of follow-up culturing.

*Bacteriologic Response Classification for Microbiologically Evaluable Isolates*

	Gatifloxacin	Ceftriaxone	Total
Eradicated	4	9	13
Presumed Eradicated	63	65	128
Persisted	1	2	3
Presumed Persisted	9	8	17
TOTAL	77	84	161

(derived from SAS transport database)

In addition, the atypical pneumonia cases that were documented were documented by serology for the most part. It is misleading to state an 100% eradication rate for *L. pneumophila* and *C. pneumoniae* because these were documented by serology only. Only 4 *M. pneumoniae* designated patients were documented by culture. For further evaluation of the atypicals see below.

Additionally, the response rates for the atypicals were based upon small numbers and therefore the comparison is not as robust as the applicant states above. Additional comments regarding the atypical pneumonia cases will be made below.

There were eighteen persistent (i.e., documented or presumed) pathogens, eight in the gatifloxacin group [*S. pneumoniae* (5), *H. influenzae* (1), *S. hominis* (1), *S. epidermidis* (1)] and nine in the ceftriaxone group [*S. pneumoniae* (2), *M. catarrhalis* (2), *S. aureus* (1), *H. influenzae* (1), *L. pneumophila* (1), *C. pneumoniae* (1), *A. baumannii* (1)]. All but two pathogens from each treatment group were presumed persisted on the basis of clinical treatment failure. The two documented persistent pathogens in the gatifloxacin group were penicillin-sensitive sputum isolates of *S. pneumoniae* from treatment failures (011-367 and 039-235; neither persistent isolate displayed altered susceptibilities. The two documented persistent pathogens in the ceftriaxone group were beta lactamase-positive *H. influenzae* and *A. baumannii* (061-393 and 055-162, respectively); the former was encountered in a clinically cured patient and the latter in a treatment failure. Neither persistent isolate displayed altered susceptibilities.

#### 8.1.2.2.2.1 NEW INFECTIONS:

Twenty-nine (14%) patients experienced new infections, 14 in the gatifloxacin arm and 15 in the ceftriaxone arm (Table 10.1.4). Respiratory tract infections, which occurred in 12 patients (six in each group), were the most common. Vaginal candidiasis occurred in five females (3 gatifloxacin, 2 ceftriaxone) and oral candidiasis was reported in four patients (1 gatifloxacin, 3 ceftriaxone). The remaining new infections were uncommon, each reported in only one or two patients.

**New Infections, Clinically Evaluable Patients  
Protocol AI420-037**

Infection Type/Diagnosis	Number of Patients (%)				
	Gatifloxacin N = 104		Ceftriaxone N = 108		Total N = 212
<u>Number of Patients Reporting Any</u>	14	(13)	15	(14)	29 (14)
<u>New Infection<sup>a</sup></u>					
Bronchitis	3		3		6
Candidiasis – vaginal	3		2		5
Candidiasis - oral	1		3		4
Candidiasis – other <sup>b</sup>	0		2		2
Upper Respiratory Infection	2		1		3
LRTI/pneumonia	1		2		3
Sinusitis	0		2		2
UTI/ kidney infection	1		1		2
Other <sup>c</sup>	3		3		6

<sup>a</sup> Patients may have more than one new infection.

<sup>b</sup> Includes presumptive disseminated candidiasis and an uncharacterized infection which was treated with nystatin.

<sup>c</sup> Other includes bursitis, diarrhea and herpes labialis in the gatifloxacin group and wound infection, bacteremia and soft tissue infection in the ceftriaxone group.

(Reference, vol 4, p 117)

**Medical Officer Comment:**

*Of interest are the 12 patients who were diagnosed with new infections related to the respiratory tract, including bronchitis Upper Respiratory Tract, LRTI/pneumonia. These infections were evenly distributed between treatment groups. The one pneumonia in each group was counted as a relapse. The Lower Respiratory Tract infection was counted as a cure, no documentation of pneumonia was seen on chest x-ray. Three patients in each group were considered to be clinical failures, as well as having a new infection which was not pneumonia. FDA review of CRFs and SAS data base is in agreement with the applicant's analysis.*

**8.1.2.2.2 RELAPSES:**

Three relapses in clinical cures occurred in the study, one in the gatifloxacin arm and two in the ceftriaxone arm. None were microbiologically documented. In the gatifloxacin case sputum at baseline grew normal flora and improvement on CXR, only to relapse on day +23 with a worsening infiltrate in the same segment.

**8.1.2.2.3 RESISTANCE ISSUES:**

Twenty-five typical pathogens (13%) were resistant to one or more study drugs according to NCCLS breakpoints. Only one isolate, (<1%) *P. aeruginosa*, was resistant to

gatifloxacin. Five isolates (3%) were resistant to ceftriaxone, and 23 isolates (12%) were resistant to clarithromycin. Four isolates were resistant to ceftriaxone and clarithromycin.

*Medical Officer Comment: the above applicant analysis was verified by FDA review of data provided.*

#### 8.1.2.2.4 ATYPICAL PNEUMONIA:

Thirty-seven atypical pathogens were identified, 18 in the gatifloxacin arm and 19 in the ceftriaxone arm. Of these patients, 10 gatifloxacin patients and seven ceftriaxone patients had a single atypical pathogen identified and no typical pathogen identified. Twenty patients (8 gatifloxacin, 12 ceftriaxone) had typical pathogens identified in conjunction with atypical pathogens.

#### Atypical Pathogens All Treated Patients Protocol AI420-037

	Number of Patients (%)	
	Gatifloxacin	Ceftriaxone
<u>Number of Patients with Atypical Pathogen</u>	18	19
Single Atypical Pathogen Only	10	7
<i>M. pneumoniae</i>	6	2
<i>C. pneumoniae</i>	2	4
<i>L. pneumophila</i>	2	1
Atypical and Typical Pathogens	8	12
<i>M. pneumoniae</i> + typical pathogen(s)	3	4
<i>C. pneumoniae</i> + typical pathogen(s)	4	3
<i>L. pneumophila</i> + typical pathogen(s)	1	5

(Reference: Vol. 4, p. 84)

The diagnosis of infection with an atypical pathogen was made by serology alone in most cases. Specific diagnostic results for each of the three atypical pathogens are as follows:

*M. pneumoniae*: Serology was the only method of diagnosis in 10 (5 gatifloxacin, 5 ceftriaxone) patients. Two of the five gatifloxacin patients had a 4-fold rise or fall in IgG titer. The remaining patients with positive serology alone had a single positive IgM or IgG titer. Four gatifloxacin patients had a positive PCR. Of those, two also had a positive culture, one also had a positive culture plus serology, and one had no additional positive diagnostic tests. One ceftriaxone patient had a positive PCR, which was associated with a positive culture and positive serology.

*C. pneumoniae*: Serology was the only method of diagnosis in all 13 (6 gatifloxacin, 7 ceftriaxone) patients. Of these 13 patients, one patient in each arm had a 4-fold or greater rise in IgG titer. The remaining patients had single positive IgG titers.

*L. pneumophila*: Serology was the only method of diagnosis in 8 (3 gatifloxacin, 5 ceftriaxone) patients. All eight had single positive IgG/M/A titers. One additional ceftriaxone patient had a positive urinary antigen test.

**Diagnosis of Atypical Pathogens, All Treated Patients  
Protocol AI420-037**

	No. of Pathogens in Patients Receiving Gatifloxacin/ Ceftriaxone		
	<i>M. pneumoniae</i>	<i>C. pneumoniae</i>	<i>L. pneumophila</i>
Total Number of Atypical Pathogens <sup>a</sup>	9/6	6/7	3/6
<u>Method of Diagnosis</u>			
Serology Only	5/5	6/7	3/5
PCR Only	1/0	0/0	0/0
PCR & Culture	2/0	0/0	0/0
Urinary Antigen	-	-	0/1
Serology & PCR & Culture	1/1	0/0	0/0

<sup>a</sup> A patient may have more than one pathogen isolated pre-treatment.  
(Reference, Vol 4, p. 85)

**Medical Officer Comment:**

*In an FDA analysis similar to that of the applicant, the overall rate of an atypical as a sole pathogen was similar (both rates = 46%). None of the patients identified with atypical pneumonia had cross-reactive serology. Combinations of atypical and "typical" pathogens were seen in roughly half of the cases reported. (see table below).*

**Microbiologically Evaluable Patients who met the Serologic Criteria for Atypical Pneumonia Pathogen**

	<i>M.pneumoniae</i> (N=11)	<i>C.pneumoniae</i> (N=10)	<i>L.pneumophila</i> (N=7)	TOTAL
Sole pathogen	6 (55 %)	4(40 %)	3(43%)	13/28 (46%)
Atypical + <i>M. pneumoniae</i>	NA	0	0	
Atypical + <i>C. pneumoniae</i>	0	NA	0	
Atypical + <i>L. pneumophila</i>	0	0	NA	
Atypical + typical path	5 (45 %)	6(60%)	4(57%)	
Note: only Atyp+Atyp	0	0	0	

FDA analysis of SAS JMP data.

*The FDA recommended that the applicant attempt to culture these pathogens as well as diagnose them by serologic methodologies. Only 4 *M. pneumoniae* were isolated by culture and only two of those patients were clinically evaluable (one in each study group). (see appendix).*

*M. Pneumoniae Infections:*

Review of *M. pneumoniae* pathogens reveals 45% of the patients had another "typical" pathogen isolated in culture. Serologic methodology which was used included PCR, and IgG / IgM by IFA (indirect fluorescent antibody). Criteria for diagnosis by the applicant per protocol were as follows:

*Mycoplasma pneumoniae* case definition (one or more of the following):

- A single IgM indirect fluorescent antibody (IFA) titer of  $\geq 1:16$  or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A single IgG indirect fluorescent antibody (IFA) titer of  $\geq 1:32$  or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive oropharyngeal PCR; and/or
- A positive oropharyngeal culture.

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits the applicant was using in these studies. Review of the test kit directions reveal the following discrepancies:

From the Zeus test kit directions for IgM provided by the applicant the interpretation/significance is as follows:

- "Fluorescence intensity of greater than +1 at the 1:16 screening dilution: Equivocal Results. Retest at a later date to evaluate the possibility of a seroconversion.
- Fluorescence intensity of greater than 1+ at 1:32 or higher: ACTIVE or CURRENT INFECTION with *M. pneumoniae*."

The applicant should have made a distinction between a single high titer which, according to the label should have been  $\geq 1:32$ , and repeat titers with a four-fold rise beginning at 1:16. Of the 11 microbiologically evaluable patients designated as *M. pneumoniae* infections, all had baseline values of  $< 1:16$ . None of the *M. pneumoniae* cases were based upon the IgM test results at baseline.

From the Zeus test kit directions for IgG provided by the applicant the interpretation/significance is as follows:

- "Fluorescence intensity of greater than +1 at the 1:32 screening dilution but not more than 1:64: Equivocal Results. PRESENT OR PAST INFECTION with *M. pneumoniae*.
  - Fluorescence intensity of greater than 1+ at 1:64 or higher: RECENT or PAST INFECTION with *M. pneumoniae*.
- \* It is recommended that in the event of borderline interpretations further testing be performed to evaluate the possibility of a later seroconversion."

The applicant should have used the criteria of greater than 1:32 rather than  $\geq 1:32$ . Four of the infections diagnosed as *M. pneumoniae* were based solely upon a titer equal to 1:32. These may not be true infections.

PCR testing is experimental at this time. However, it had good correlation with the *M. pneumoniae* cultures. All 4 patients with culture positive *M. pneumoniae* had Positive PCR tests.

Overall, the number of infections due to *M. pneumoniae* may be somewhat less than the applicant states, given the above analysis. All of the patients were clinically cured. Therefore, each study drug may be highly efficient in treating this pathogen, OR as the majority of cases of *M. pneumonia* resolve without treatment it may be difficult to attribute the exact clinical response rate in this circumstance.

Regarding the Bacteriologic response of *M. pneumonia*, only 2 microbiologically evaluable patients had initial isolate from culture. Follow-up information on these isolates was not provided by the applicant, therefore, the only response could be presumed eradicated based upon clinical cure. Because the diagnosis for the majority was made on a serologic basis, it would be inaccurate to describe the pathogen as being eradicated. However, based upon the definition in the protocol one could designate them as being presumed eradicated.

#### **C. pneumoniae:**

Review of *C. pneumoniae* infections reveals that 60% of patients had another typical pathogen isolated in culture. Serologic methodology which was used included PCR, IgM and IgG by IFA. Criteria for diagnosis by the applicant per protocol was as follows:

##### *Chlamydia pneumoniae* case definition (one or more of the following):

- A single IgM indirect fluorescent antibody (IFA) titer of  $\geq 1:10$  or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A single IgG indirect fluorescent antibody (IFA) titer of  $\geq 1:512$  or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive oropharyngeal PCR; and/or
- A positive oropharyngeal culture.

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits the applicant was using in these studies. Review of the test kit directions reveal the following discrepancies:

From the MRL Diagnostics' test kit directions for IgM provided by the applicant the interpretation/significance is as follows:

- "IgM endpoint titers of 1:20 and greater are considered presumptive evidence of infection.
- IgM endpoint titers less than 1:20 suggest that the patient does not have a current infection. This may be found in patients with either no history of Chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels."

The applicant should have utilized the level of  $\geq 1:20$  and not  $\geq 1:10$  according to the package insert. All but one patient designated as having *C. pneumoniae* had IgM titers

of <10 which did not change upon subsequent testing. None of the diagnosis were made solely on the basis of this titer.

From the MRL Diagnostics' test kit directions for IgG provided by the applicant the interpretation/significance is as follows:

For C. pneumoniae:

- "IgG endpoint titers of  $\geq 1:512$  and greater are considered presumptive evidence of current infection."
- A single specimen endpoint titer  $\geq 1:64$  and  $< 1:512$  should be considered evidence of infection at an undetermined time. A second specimen drawn 10 to 21 days after the original draw should be tested in parallel with the first. IF the second specimen exhibits a titer  $\geq 1:512$  or a four fold increase over that of the initial specimen, current (acute) infection is indicated. Unchanging titers  $\geq 1:64$  and  $< 1:512$  suggest past infection.
- IgG endpoint titers less than 1:64 suggest that the patient does not have a current infection. This may be found in patients with either no history of Chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels."

*The applicant applied the test kit criteria correctly for the IgG.*

*PCR testing is experimental at this time. In this group of pathogens there were not C. pneumoniae isolated by culture. None of the patients had positive PCR results for C. pneumoniae.*

*Overall the number of infections with C. pneumoniae was based solely upon serologic diagnosis. Only 1 patient was designated as clinical Failure (in the ceftriaxone). Gatifloxacin appears to be equally efficacious in treating C. pneumoniae as ceftriaxone.*

*Three of 5 patients in each group had a "typical" pathogen diagnosed in the sputum as well.*

*Regarding Bacteriologic response for C. pneumoniae, no cultures were positive for this organism, hence the outcome is based upon the clinical outcome and would be classified as presumed eradicated. It would be inaccurate to describe a bacteriologic response for this pathogen as eradicated.*

**L. pneumophila:**

*Review of L. pneumophila infections reveals 57% of the patients had another "typical" pathogen isolated in culture. Serologic methodology which was used included PCR, Combined Titer, and Urinary Antigen Testing. None of the PCR tests were positive and only one of the Urinary Antigen tests was positive. Criteria for diagnosis by the applicant per protocol were as follows:*

- "Legionella pneumophila case definition (one or more of the following):

- A single IgG/M/A indirect fluorescent antibody (IFA) titer of  $\geq 1:256$  or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive urine antigen test;
- A positive oropharyngeal PCR for *Legionella sp.*; and/or
- A positive oropharyngeal culture."

*These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits that the applicant was using in these studies.*

*Review of the test kit insert for the combined titer reveals the following:*

- "A four-fold rise in titer  $\geq 1:128$  from the acute to the convalescent phase provides evidence of a recent infection with *Legionella*.
- A standing or single titer  $\geq 256$  provides presumptive evidence of infection at an undetermined time.
- Single titers of less than 256 are not considered evidence of infection."

*The criteria the applicant used to evaluate *L. pneumophila* infection are in agreement with the recommendations in the package insert regarding combined titers.*

*All of the patients designated as having *L. pneumophila* infections met the serologic criteria for presumed infection. One patient had descending titers. Only one patient was designated as to have failed clinically (in the ceftriaxone group). This patient had other atypical pathogens isolated from sputum (*S. aureus*, *S. pneumoniae*).*

*None of the patients designated as having *L. pneumophila* infection had a positive PCR screen. Only one patient had a positive urinary antigen, but also had *S. pneumoniae*, *P. aeruginosa* and *A. baumannii* isolated in the sputum the Combined titer was  $< 256$ . This patient was listed as being cured and was in the ceftriaxone group.*

*Overall, the cure rate was similar between treatment groups. Regarding the Bacteriologic response of *L. pneumophila*, it can only be based upon serologic diagnosis as none of the cases had an culture proven infection. Thus, according to the protocol the patients could be designated as presumptive eradication. It would be inaccurate to describe the pathogen as being eradicated without culture documentation.*

#### Summary of Atypical Pneumonia review:

*The overall analysis by the applicant may over represent the number of cases due to atypical pathogens. While serology may be applied to identify potential cases, additional serology is necessary given the uncertainty of the interpretation of test results. The FDA analysis is represented in the table below. Of the cases reported by the applicant, those listed in the table below may represent the cases most likely to have had community acquired pneumonia due to the atypical pathogens listed. The body of evidence required for these pathogens should err on the side of conservatism, especially in the case of *L. pneumophila*. Legionnaires' Disease has a high mortality rate, and in order to support*

the inclusion of this pathogen in the label it is important to include well documented cases.

**Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin  
According to Diagnostic Criteria**

	<i>M. pneumoniae</i>	<i>C. pneumoniae</i>	<i>L. pneumophila</i>
Culture positive (PCR):	2	0	0
Definitive (4X rise in IgG or IgM)	0	1	0
Presumptive (single high titer)	3	1	2
Urinary Antigen	NA	NA	0
<b>TOTAL</b>	<b>5</b>	<b>2</b>	<b>2</b>

\* note: test kit recommendations for single high titer are used in this analysis, in addition these categories are mutually exclusive (eg. If case is culture positive it is not counted in the serologic category) Also, patients may carry the diagnosis of more than one atypical. Cases may not have another "typical" pathogen isolated in the baseline sputum unless atypical culture was positive or case had definitive serology.

FDA analysis reveals that cases of atypical pneumonia on the gatifloxacin treatment arm included 5 cases of *M. pneumoniae*, 3 cases of *C. pneumoniae*, and 2 cases of *L. pneumophila pneumonia*, which were documented according to strict criteria. All of these cases were considered clinical cures. As is noted in the table above, most of these infections were diagnosed upon the basis of a single high titer.

It is difficult to evaluate the true efficacy of gatifloxacin with regard to atypical pneumonia cases that were only documented by serology. *M. pneumoniae* has a clinical course that is somewhat different than *C. pneumoniae* and *L. pneumophila*. It may take a month or two for the symptoms to resolve even with treatment. A prospective study of each individual disease entity would be most informative with regard to efficacy. Culture is still the gold standard.

Given the data presented by the applicant and the problems inherent in diagnosis by serology, it appears that gatifloxacin is active against these pathogens.

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**8.1.2.3. SAFETY RESULTS:****8.1.2.3.1 Overall and Related Adverse Clinical Events:**

Overall, two hundred sixty-one (92%) patients experienced one or more adverse clinical event. All adverse clinical events (94 % ceftriaxone, 91% gatifloxacin). Drug-related adverse clinical events (56% ceftriaxone vs. 49% gatifloxacin) occurred at a higher rate in the ceftriaxone arm. Most notable among these were the following drug-related gastrointestinal adverse events: diarrhea (13% vs. 6%), vomiting (6% vs. 2%), taste perversion (7% vs. 4%), dyspepsia (6% vs. 3%) and abdominal pain (4% vs. <1%) were all more common in ceftriaxone-treated patients. The frequency of IV site reactions in the two groups was comparable.

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**Adverse Clinical Events of All Causes by Relationship to Study Medication, All Treated Patients  
Protocol A1420-037**

Adverse Clinical Event	Number of Patients (%)															
	Gatifloxacin N = 141								Ceftriaxone N = 142							
	Related		Unknown Relationship		Not Related		Total		Related		Unknown Relationship		Not Related		Total	
<b>Any Adverse Clinical Event</b>	69	(49)	4	(3)	55	(39)	128	(91)	80	(56)	5	(4)	48	(34)	133	(94)
Abnormal Breath Sounds	3	(2)	-		47	(33)	50	(35)	-		1	(<1)	59	(42)	60	(42)
Increased Sputum	3	(2)	-		15	(11)	18	(13)	1	(<1)	-		12	(8)	13	(9)
Nausea	15	(11)	-		4	(3)	19	(13)	15	(11)	-		5	(4)	20	(14)
Chest Pain	3	(2)	-		14	(10)	17	(12)	-		-		15	(11)	15	(11)
Constipation	10	(7)	-		6	(4)	16	(11)	7	(5)	2	(1)	9	(6)	18	(13)
Insomnia	6	(4)	-		7	(5)	13	(9)	6	(4)	1	(<1)	12	(8)	19	(13)
Coughing	2	(1)	-		11	(8)	13	(9)	-		-		14	(10)	14	(10)
Headache	1	(<1)	-		11	(8)	12	(9)	6	(4)	1	(<1)	8	(6)	15	(11)
Peripheral Edema	1	(<1)	1	(<1)	10	(7)	12	(9)	1	(<1)	-		9	(6)	10	(7)
Dyspnea	2	(1)	-		9	(6)	11	(8)	-		1	(<1)	16	(11)	17	(12)
Confusion	4	(3)	1	(<1)	6	(4)	11	(8)	2	(1)	-		2	(1)	4	(3)
Fever	1	(<1)	-		10	(7)	11	(8)	-		1	(<1)	14	(10)	15	(11)
Disorder (Respiratory)	-		-		10	(7)	10	(7)	1	(<1)	1	(<1)	8	(6)	10	(7)
Pain	1	(<1)	1		9	(6)	10	(7)	-		-		10	(7)	10	(7)

Indication: Community Acquired Pneumonia (Study 037)

Revision Date: 22-Nov-99

Adverse Clinical Event	Number of Patients (%)														
	Gatifloxacin N = 141							Ceftriaxone N = 142							
	Related		Unknown Relationship	Not Related		Total	Related		Unknown Relationship	Not Related		Total			
Diarrhea	8	(6)	-	2	(1)	10	(7)	19	(13)	1	(<1)	2	(1)	22	(15)
Taste Perversion	5	(4)	-	-		5	(4)	10	(7)	-		-		10	(7)
Abdominal Pain	1	(<1)	-	4	(3)	5	(4)	5	(4)	-		5	(4)	10	(7)
Asthenia	-		-	5	(4)	5	(4)	1	(<1)	1	(<1)	7	(5)	9	(6)
Vomiting	3	(2)	-	6	(4)	9	(6)	8	(6)	-		7	(5)	15	(11)
Malaise	1	(<1)	-	8	(6)	9	(6)	2	(1)	-		6	(4)	8	(6)
Hypotension	-		-	6	(4)	6	(4)	2	(1)	1	(<1)	4	(3)	7	(5)
Reaction IV Site	12	(9)	-	4	(3)	16	(11)	13	(9)	1	(<1)	3	(2)	17	(12)
Dyspepsia	4	(3)	-	4	(3)	8	(6)	8	(6)	-		1	(<1)	9	(6)
Anxiety	3	(2)	-	4	(3)	7	(5)	3	(2)	-		6	(4)	9	(6)

<sup>a</sup> All adverse clinical events occurring in >5% of the total number of treated patients.  
(Source: vol 4, P 125)

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**Drug-Related Adverse Clinical Events by Severity of Event, All Treated Patients  
Protocol A1420-037**

Adverse Clinical Event <sup>a</sup>	Number of Patients (%)									
	Gatifloxacin N = 141					Ceftriaxone N = 142				
	Mild	Moderate	Severe	Very Severe	Total	Mild	Moderate	Severe	Very Severe	Total
<b>Any Related Adverse Clinical Event</b>	29 (21)	35 (25)	3 (2)	2 (1)	69 (49)	37 (26)	36 (25)	7 (5)	-	80 (56)
Reaction IV Site	10 (7)	2 (1)			12 (9)	9 (6)	3 (2)	1 (<1)		13 (9)
Headache	-	1 (<1)	-	-	1 (<1)	6 (4)	-	-	-	6 (4)
Constipation	5 (4)	5 (4)	-	-	10 (7)	4 (3)	3 (2)	-	-	7 (5)
Diarrhea	7 (5)	1 (<1)	-	-	8 (6)	11 (8)	8 (6)	-	-	19 (13)
Dyspepsia	1 (<1)	3 (2)	-	-	4 (3)	5 (4)	3 (2)	-	-	8 (6)
Oral Moniliasis	3 (2)	1 (<1)	-	-	4 (3)	4 (3)	2 (1)	-	-	6 (4)
Nausea	7 (5)	6 (4)	2 (1)	-	15 (11)	7 (5)	6 (4)	2 (1)	-	15 (11)
Abdominal Pain	-	1 (<1)	-	-	1 (<1)	2 (1)	1 (<1)	2 (1)	-	5 (4)
Vomiting	1 (<1)	1 (<1)	1 (<1)	-	3 (2)	4 (3)	3 (2)	1 (<1)	-	8 (6)
Anxiety	2 (1)	1 (<1)	-	-	3 (2)	2 (1)	1 (<1)	-	-	3 (2)
Confusion	2 (1)	2 (1)	-	-	4 (3)	1 (<1)	1 (<1)	-	-	2 (1)
Insomnia	1 (<1)	5 (4)	-	-	6 (4)	3 (2)	3 (2)	-	-	6 (4)
Rash	2 (1)	1 (<1)	-	-	3 (2)	3 (2)	1 (<1)	-	-	4 (3)
Taste Perversion	5 (4)	-	-	-	5 (4)	6 (4)	4 (3)	-	-	10 (7)

<sup>a</sup> All drug-related adverse clinical events occurring in >2% of the total number of treated patients.  
(Reference: vol 4, p 128)

**Medical Officer Comment:**

FDA review of the safety data provided by the applicant in the SAS transport files and the CRFs is in agreement the applicant's analysis. The applicant tables included above include the events which occurred most frequently, at a rate of > 5%. It is of interest to note less commonly occurring events of interest such as those related to the quinolone class effects, eg. dizziness, insomnia, arrhythmia or dysrhythmias, phototoxicity, tendon rupture. The medical officer will comment on these below.

No cases of pancreatitis were reported.

Review of the Gastrointestinal System found that nausea and vomiting were the most frequently occurring events and the rates were similar in both treatment groups, but slightly less in the gatifloxacin group. More discontinuations due to severe nausea/vomiting were seen in the ceftriaxone group (4 patients) versus the gatifloxacin group (2 patients). Four patients were reported in the AE section to have elevated liver function tests (gatifloxacin = 1 patient vs. ceftriaxone = 3 patients). These abnormalities were all mild in nature. The gatifloxacin patient had renal cell carcinoma and pulmonary emboli diagnosed. (further discussion of liver function tests is located in the laboratory abnormalities section).

Among the Nervous System events of interest (dizziness, insomnia, and confusion). Insomnia was seen equally in both arms, slightly more frequently in the ceftriaxone group, and the events were mild or moderate and the patients were not discontinued because of this reaction. Dizziness was seen in both treatment groups to a similar degree (two cases each). These events were reported to be mild to moderate. Of the related events, neither could be explained by the laboratory studies (eg no hypoglycemia documented). There were no seizures reported in this study. There was one paranoid reaction seen in the gatifloxacin group but this was thought by the investigator to be due to the steroids.

Review of the Cardiovascular System revealed more events in the ceftriaxone group than the gatifloxacin group. There were reports of arrhythmias in each group. Of the related arrhythmias there were 2 patients in the gatifloxacin group and 8 patients in the ceftriaxone group. One gatifloxacin patient (78-338) had an ECG which reported atrial, sinus tachyarrhythmia which resolved. The patient was on concomitant aminophylline. The second patient was noted to have a racing pulse which was recorded at 100. This also resolved without incident.

**8.1.2.3.2 Discontinuation Due to Adverse Clinical Events:**

Twelve patients in the ceftriaxone arm and eleven patients in the gatifloxacin arm discontinued study therapy because of an adverse event or laboratory abnormality. Of the laboratory abnormality discontinuations in the gatifloxacin arm one was due to worsening hypernatremia and one due to hyperglycemia. Nine of the ceftriaxone discontinuations were felt to be drug-related; seven of these were due to one or more gastrointestinal AE. Six discontinuations in the gatifloxacin arm were felt to be related to study drug and two of the six were due to one or more gastrointestinal AE.

**Medical Officer Comment:**

*FDA review of the safety data provided by the applicant in the SAS transport files and CRFs is in agreement with the applicant's analysis. Of interest are the less frequent reasons for discontinuation. In the gatifloxacin group one patient had a paranoid reaction which was described above. Another had agitation and confusion but it was unclear if this was due to the study drug. There was one patient in the ceftriaxone group that had medication discontinued because of hallucinations.*

**8.1.2.3.3 Serious Adverse Events and Deaths:**

Fifty-three patients experienced serious adverse events (SAE) on study, six of which were felt by the Investigator to be study drug-related (4 gatifloxacin, 2 ceftriaxone). Only two of these, however, were felt by the blinded applicant's medical monitor to be study drug-related. The most frequent SAEs were those involving the respiratory system and were almost exclusively felt to be related to underlying disease.

Twelve deaths occurred within 30 days of end of treatment (gatifloxacin-7, ceftriaxone-5) and three deaths occurred beyond 30 days after end of treatment (gatifloxacin-1, ceftriaxone-2). None were study drug-related. Two patients in each arm were felt to have died from underlying disease. These included COPD (037-025), CHF (078-339), myocardial infarction and CHF (038-178) and CHF with severe hypotension (048-116).

Five patients in the gatifloxacin arm were felt to have died from underlying disease plus their primary infection. Two of these patients were previously described: Patient 011-368 with acute leukemia who developed empyema due to *S. pneumoniae* requiring intubation and vasopressors; and patient 053-298 with diabetes, chronic renal insufficiency and bacteremic *H. influenzae* pneumonia. The other three gatifloxacin patients, all with underlying COPD, were from site 071: patient 071-195 received only one dose of IV gatifloxacin and died the next day of group A streptococcal sepsis; patient 071-489 withdrew from the study and refused further heroic measures after four days of therapy in the ICU for severe pneumonia due to *S. pneumoniae* and *M. catarrhalis*; and patient 071-534 died from a COPD exacerbation precipitated by a rib fracture on Day +3 after a 14-day course of therapy in the ICU for severe pneumonia due to *K. pneumoniae* and *S. aureus*. A chest radiograph at the time of rehospitalization showed resolution of the pneumonia.

There were three other deaths in the ceftriaxone arm. Patient 008-008 developed a cardiopulmonary arrest (torsades-de-pointes rhythm) after 3 days of therapy and died of a second cardiac arrest four days later (underlying disease, "pneumonia" plus primary infection). Patient 064-103, with chronic alcohol abuse and dysphagia, died of "aspiration pneumonia" 21 days after failing a seven-day course of therapy for severe pneumonia due to *S. pneumoniae*, *M. catarrhalis* and *P. fluorescens* (primary infection plus underlying disease plus new infection). Lastly, patient 011-260 developed an anaerobic wound infection and required treatment for presumed disseminated fungal infection after failing an eight-day course of ceftriaxone plus erythromycin for severe pneumonia. She expired on Day +7 from multisystem organ failure ("not indicated").

Three additional patients expired after Day +30, one in the gatifloxacin arm (033-176) and two in the ceftriaxone arm (043-343, 057-379).

**Deaths Within 30 Days of End of Treatment,  
All Treated Patients  
Protocol AI420-037**

	Number of Patients		
	Gatifloxacin N = 141	Ceftriaxone N = 142	Total N = 283
Number of Deaths	7	5	12
<u>Cause of Death</u>			
Underlying Disease	2	2	4
Primary infection + Underlying Disease	5	1	6
Primary infection + Underlying Disease	-	1	1
+ New Infection			
Not indicated	-	1	1

(Reference vol 4, p129-30)

**Medical Officer Comment:**

*It should be noted that in comparison to the CAP study 002, these patients were sicker upon entry into the study and were hospitalized. This may be the reason for the larger, overall, number of serious adverse events and deaths in this study. Review of Data supplied by the applicant is in agreement with the applicant's analysis.*

**8.1.2.3.4 Local IV tolerance:**

Twenty-three (23) percent of gatifloxacin patients and 20% of ceftriaxone patients experienced local intolerance to IV study drug. Not all IV site reactions were captured on the CRF as an AE; thus, the number of patients experiencing local intolerance is higher than the number of patients with an AE of "IV site reaction." The frequency of intolerance by individual category was similar in the two treatment arms. Of note, 13/142 patients receiving the ceftriaxone regimen who experienced intolerance also received IV erythromycin. The most common manifestations of intolerance were infiltration (12 episodes in each group), followed by redness at the IV site (8 gatifloxacin, 7 ceftriaxone). The two gatifloxacin-treated patients with "other" local intolerance include one patient (071-534) whose IV catheter was flushed with saline and would not restart and another patient (011-368) with ecchymosis at the IV site.

**Local IV Intolerance, All Treated Patients  
Protocol A1420-037**

	Number of Patients (%)			
	Gatifloxacin N = 141		Ceftriaxone N = 142	
<u>Tolerated Study Drug Well</u>	108	(77)	114	(80)
Local Intolerance <sup>a</sup>	33	(23)	28	(20)
Infiltration	12	(9)	12	(8)
Redness	8	(6)	7	(5)
Pain	8	(6)	4	(3)
Discomfort/tenderness	6	(4)	5	(4)
Burning	-		4	(3)
Phlebitis	1	(<1)	1	(<1)
Induration	1	(<1)	-	
Swelling/edema	5	(4)	3	(2)
Pruritus	3	(2)	-	
Other	2	(1)	-	

<sup>a</sup> Patients may have experienced more than one type of intolerance.  
(Reference, vol 4, p 139)

**Medical Officer Comment:**

*From the data presented, it would appear that gatifloxacin infusion is tolerated as well as the control group.*

**8.1.2.3.5 Laboratory Abnormalities:**

In patients with normal pre-treatment laboratory values, decreased hemoglobin and elevated transaminases (i.e., ALT, AST) were the during- or post-treatment abnormalities most frequently noted in both groups. Elevated transaminases were more frequently noted in the ceftriaxone arm. Ten patients (6 gatifloxacin, 4 ceftriaxone) developed a Grade 3 abnormality and two gatifloxacin patients developed a Grade 4 abnormality. In patients with abnormal pre-treatment laboratory values, the majority worsened only to Grade 2. Twelve patients worsened to Grade 3 (7 ceftriaxone, 5 gatifloxacin) and two gatifloxacin patients worsened to Grade 4.

**Abnormal Laboratory Test Values During or Post-Treatment in Patients with  
Normal Pre-treatment Values, All Treated Patients  
Protocol A1420-037**

Laboratory Test	Number of Patients (%)									
	Gatifloxacin					Ceftriaxone				
	Na	Grade 1	Grade 2	Grade 3	Grade 4	Na	Grade 1	Grade 2	Grade 3	
Hemoglobin	53	19 (36)	-	-	-	57	29 (51)	1 (2)	-	
WBC	108	4 (4)	4 (4)	-	-	103	7 (7)	-	1 (<1)	
Neutrophils	108	6 (6)	3 (3)	1 (<1)	-	99	7 (7)	1 (1)	1 (1)	
Platelets	92	9 (10)	-	-	-	76	5 (7)	-	-	
Alkaline Phosphatase	96	9 (9)	-	-	-	93	11 (12)	-	-	
AST	93	18 (19)	1 (1)	-	-	84	22 (26)	-	1 (1)	
ALT	105	13 (12)	-	1 (<1)	-	96	21 (22)	1 (1)	-	
Total Bilirubin	99	-	1 (1)	1 (1)	-	88	-	1 (1)	1 (1)	
BUN/Urea	90	11 (12)	1 (1)	-	-	82	16 (20)	-	-	
Creatinine	95	7 (7)	-	-	-	91	2 (2)	1 (1)	-	
Glucose Decrease (fasting)	4	-	-	-	-	1	-	-	-	
Glucose Increase (fasting)	4	3 (75)	-	-	-	1	1 (100)	-	-	
Amylase	108	5 (5)	-	2 (2)	1 (<1)	96	6 (6)	1 (1)	1 (1)	
Hyponatremia	90	11 (12)	1 (1)	-	-	81	10 (12)	-	-	
Hypernatremia	90	4 (4)	-	-	-	81	10 (12)	1 (1)	-	

Indication: Community Acquired Pneumonia (Study 037)

Revision Date: 22-Nov-99

Laboratory Test	Number of Patients (%)									
	Gatifloxacin					Ceftriaxone				
	Na	Grade 1	Grade 2	Grade 3	Grade 4	Na	Grade 1	Grade 2	Grade 3	
Hypokalemia	92	10 (11)	-	-	-	83	5 (6)	-	-	
Hyperkalemia	92	4 (4)	-	-	-	83	3 (4)	-	-	
Hypochloremia	108	4 (4)	1 (<1)	1 (<1)	1 (<1)	94	4 (4)	1 (1)	-	
Hyperchloremia	108	9 (8)	-	-	-	94	5 (5)	-	-	
Decreased Bicarbonate	52	12 (23)	-	1 (2)	-	52	14 (27)	1 (2)	-	
Increased Bicarbonate	52	6 (12)	-	-	-	52	5 (10)	3 (6)	-	

<sup>a</sup> For each test, number of patients with a normal pre-treatment value who had at least one during or post-treatment value determined.  
(Reference vol 4, p142)

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**Worsened Laboratory Test Values During or Post-Treatment in Patients with  
Abnormal Pre-treatment Values, All Treated Patients  
Protocol A1420-037**

Laboratory Test	Number of Patients (%)							
	Gatifloxacin				Ceftriaxone			
	Na	Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4	Na	Worsened to Grade 2	Worsened to Grade 3	
Hemoglobin	59	9 (15)	3 (5)	-	47	4 (9)	-	
WBC	4	-	-	-	2	-	-	
Neutrophils	2	-	-	-	0	-	-	
Platelets	20	-	-	-	27	-	-	
Alkaline Phosphatase	16	-	-	-	10	-	-	
AST	19	2 (11)	-	-	20	2 (10)	2 (10)	
ALT	7	-	-	-	6	-	-	
Total Bilirubin	11	-	-	-	16	-	-	
BUN/Urea	23	1 (4)	-	-	26	2 (8)	-	
Creatine	18	1 (6)	-	-	17	-	-	
Glucose Decrease (fasting)	6	-	-	-	1	-	-	
Glucose Increase (fasting)	6	1 (17)	-	-	1	-	-	
Amylase	3	-	-	-	4	-	2 (50)	
Hyponatremia	23	2 (9)	1 (4)	-	27	1 (4)	-	
Hypernatremia	23	-	-	1 (4)	27	-	-	

Indication: Community Acquired Pneumonia (Study 037)

Revision Date: 22-Nov-99

Laboratory Test	Number of Patients (%)							
	Gatifloxacin				Ceftriaxone			
	Na	Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4	Na	Worsened to Grade 2	Worsened to Grade 3	
Hypokalemia	21	1 (5)	-	-	25	1 (4)	-	
Hyperkalemia	21	-	-	-	25	-	-	
Hypochloremia	3	-	-	-	14	1 (7)	-	
Hyperchloremia	3	-	-	-	14	-	-	
Decreased Bicarbonate	61	3 (5)	-	-	56	2 (4)	1 (2)	
Increased Bicarbonate	61	-	1 (2)	1 (2)	56	1 (2)	2 (4)	

<sup>a</sup> For each test, number of patients with an abnormal pre-treatment value who had at least one during or post-treatment value determined.  
(Reference, Vol. 4, 145)

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**Patients with Normal Pre-treatment Values**

Abnormal laboratory values noted during- or post-treatment in patients with normal pre-treatment values were generally mild (Grade 1). With few exceptions, both the severity and frequency were not substantially different between the two treatment groups. One exception was transaminases--more Grade 1 ALT (22 vs. 12) and AST (26 vs. 19) abnormalities occurred with ceftriaxone than with gatifloxacin. There were 11 Grade 2 abnormalities in each group, two of which in each group were in ALT, AST, or bilirubin.

Ten Grade 3 abnormalities occurred, six in the gatifloxacin arm and four in the ceftriaxone arm. The six gatifloxacin abnormalities included elevated amylase (232 U/L, 281 U/L) in two patients, elevated ALT (672 U/L) noted on Day +1 and resolved at Day +17, transient neutropenia, hyperchloremia and decreased bicarbonate. The four ceftriaxone abnormalities included elevated AST (202 U/L) noted on Day 4 resolved at Day +13, elevated amylase (399 U/L), leukopenia and neutropenia. Two Grade 4 abnormalities occurred, both in gatifloxacin-treated patients. Patient 024-081 had a normal amylase from the pre-treatment visit through Day +11. On Day +28, however, he was noted to have an amylase of 1405 U/L in the setting of vomiting. A subsequent workup revealed cholelithiasis and a history of alcohol abuse. The Investigator believed this syndrome to be pancreatitis related to either gallstones or alcohol. A follow-up amylase on Day +31 was 192 U/L. Patient 025-292 had a serum chloride which decreased from a pre-treatment value of 95 mEq/L to 82 mEq/L at the time of discontinuation on Day 7. Although not noted by the Investigator in relation to hypochloremia, the patient was discontinued for stupor on Day +1, the day after the hypochloremia was noted.

*Medical Officer Note: It should be noted that this case of pancreatitis was not entered into the adverse event database by the investigator, and therefore not counted in that dataset.*

**Patients with Abnormal Pre-treatment Values**

There were 48 occurrences of worsening of an abnormal pre-treatment laboratory value, 27 in the gatifloxacin arm and 21 in the ceftriaxone arm. The majority worsened only to Grade 2. Seven patients in the ceftriaxone group and five patients in the gatifloxacin group had abnormal pre-treatment values which worsened to Grade 3. The seven in the ceftriaxone group included two patients with increased AST (69 U/L to 222 U/L and 107 U/L to 213 U/L), two patients with increased amylase (167 U/L to 246 U/L and 218 U/L to 339 U/L), two patients with increased bicarbonate and one patient with decreased bicarbonate. The five in the gatifloxacin group included three patients with decreased hemoglobin, one patient with worsened hyponatremia and one patient with increased bicarbonate. Two gatifloxacin patients had abnormal pre-treatment values which worsened to Grade 4. One patient (025-292) was discussed in section 12.7.1, and experienced an increase in serum bicarbonate from Grade 3 to Grade 4 contemporaneously with stupor. The other patient (053-141) experienced worsening of hypernatremia from Grade 2 to Grade 4 and was discontinued.

**Medical Officer Comment:**

It is of interest to note that the grade 2/3 AST/ALT liver abnormalities which occurred in the patients with normal baseline tests occurred in the same patient. It occurred in one patient in the gatifloxacin arm and one patient in the ceftriaxone arm had grade 2/3 AST/ALT elevations. Neither had a change in their total bilirubin. Patients with normal baseline liver function tests developed elevated total bilirubins in both treatment arms (gatifloxacin = 2 patients vs. ceftriaxone = 4 patients). Concomitant elevation in ALT/AST occurred in one patient in each group. These were mild grade abnormalities. Two patients in the gatifloxacin arm and 6 patients in the ceftriaxone arm had increases in ALT/AST to two times the upper limit of normal. None of the gatifloxacin patients had concomitant total bilirubin increases. One of these patients had metastatic cancer.

None of the 46 patients with fasting blood sugar results at baseline had hypoglycemia documented during the study. Of the two patients in the gatifloxacin arm who had grade 2 amylase increases, one of them was documented to have metastatic renal cell carcinoma, the other had diabetes mellitus. Neither had a clinically diagnosed pancreatitis.

**8.1.2.3.6 Medical Officer Safety Summary:**

The most frequent adverse events were related to the gastrointestinal system, excluding those which may be related to pneumonia. These rates were similar when gatifloxacin was compared to ceftriaxone. Numerically, nausea, vomiting and diarrhea were reported less frequently in the gatifloxacin treatment group as compared to the ceftriaxone group. The adverse events as a result of the intravenous infusion were minimal and similar to that of ceftriaxone. Fewer gatifloxacin patients discontinued study drug due to gastrointestinal adverse clinical events than in the ceftriaxone group. A similar number of deaths occurred in both treatment groups. In this study of patients hospitalized with community acquired pneumonia, more deaths occurred as compared to Study 002, and the reasons for death were mostly related to underlying disease and not study drug. Elevations in liver function tests were noted and were mild in nature, occurring somewhat more frequently in the ceftriaxone treatment group. Ceftriaxone is known to have this effect. There were only two patients in each treatment group that had normal liver function tests at baseline who subsequently developed an abnormal total bilirubin of a mild nature. Only one in each group had a concomitant elevation in AST/ALT. These patients had histories of alcohol/drug abuse. IV infusion was equally well tolerated when both treatment groups were compared.

There were no class related events reported in this study including phototoxicity, tendon rupture, seizures, hypoglycemia, HUS or torsades de pointe in the gatifloxacin treatment group. One case of torsades-de-pointe was reported in the ceftriaxone treatment group.

Gatifloxacin appears to be equally well tolerated in comparison to ceftriaxone in the treatment of Community Acquired Pneumonia patients who require hospitalization.

**8.1.2.4 OVERALL CONCLUSIONS:**

**APPLICANT'S CONCLUSIONS:** The results of this study demonstrate that gatifloxacin 400 mg IV once daily +/- step-down to gatifloxacin 400 mg PO once daily for 7-14 days, is as safe and efficacious as ceftriaxone 1-2 gm IV once daily (with or without IV erythromycin) +/- step-down to clarithromycin 500 mg PO twice daily for 7-14 days, in the treatment of mild to moderate and severe community-acquired pneumonia requiring hospitalization. (DATE OF REPORT: 10-December-1998.)

#### **MEDICAL OFFICER SUMMARY OF SAFETY AND EFFICACY FOR STUDY 037:**

This double-blind, randomized, controlled study demonstrated the efficacy of gatifloxacin, given at a dose of gatifloxacin 400 mg QD (IV to PO or IV only) x 7 to 14 days; v.s. ceftriaxone 1-2 gm QD with or without erythromycin Q6H (IV to clarithromycin 500 mg BID PO or IV only) x 7 to 14 days. The cure rates were somewhat higher for the gatifloxacin treated patients in comparison to the ceftriaxone treated patients (88% vs. 85% , respectively in the clinically evaluable patients [95% C.I. -7.6%, 15.3%]. The difference in cure rates remained stable among the various analysis groups (All Treated Patients, Clinically Eligible). There was a significant amount of missing data in this study, probably due to the severity of illness in this study. The patients in this study were treated as inpatients and were considered to be more severely ill in comparison to those enrolled in study 002. The cure rates in both studies for gatifloxacin in the evaluable patient cohort were similar, although in this study the cure rate for gatifloxacin was somewhat higher than that for ceftriaxone.

#### **Applicant Clinical Efficacy Analysis (Study 037) (Cure rates)**

Subgroup	Gatifloxacin	Ceftriaxone	Confidence Interval
All Treated Patients (N=287)	73% (102/141)	70% (103/142)	-8.4%, 14.8%
Eligible Patients	74% (100/136)	71% (99/140)	-8.5%, 15.0%
Evaluable Patients	88% (92/104)	85% (92/108)	-7.6%, 15.3%

With regard to microbiologically documented infections, as would be expected in a pneumonia study, slightly more than half of the patients enrolled did not have a baseline pathogen identified in the sputum. Adequate numbers of *S. pneumoniae* and *H. influenzae* were successfully treated in this study, supporting the proposed label. *M. catarrhalis*, *S. aureus*, *K. pneumoniae* and *H. parainfluenzae* were not represented in adequate numbers and will have to be considered in total, across the CAP studies. Only one patient was documented to have penicillin resistant *S. pneumoniae* in the baseline sputum. This patient was cured. This case by itself is not enough evidence for to support the efficacy of gatifloxacin for the treatment of *S. pneumoniae* (penicillin-resistant). This issue will be considered in the overall summary of CAP, where cases are collected from all five trials submitted to the NDA.

**FDA Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin  
According to Diagnostic Criteria**

	<b>M. pneumoniae</b>	<b>C. pneumoniae</b>	<b>L. pneumophila</b>
Culture positive (PCR)	2	0	0
Definitive (4X rise in IgG or IgM)	0	1	0
Presumptive (single high titer)	3	1	2
Urinary Antigen	NA	NA	0
<b>TOTAL</b>	<b>5</b>	<b>2</b>	<b>2</b>

*\* note: test kit recommendations for single high titer are used in this analysis, in addition these categories are mutually exclusive (eg. If case is culture positive it is not counted in the serologic category) Also, patients may carry the diagnosis of more than one atypical. Cases may not have another "typical" pathogen isolated in the baseline sputum unless atypical culture was positive or case had definitive serology.*

Atypical pneumonia was diagnosed by serology for the most part. When stricter FDA criteria were applied the number of cases treated with each pathogen were lower than that stated by the applicant. *M. pneumoniae* was isolated in culture from 2 patients treated with gatifloxacin which were clinically evaluable. A total of 3 patients in the gatifloxacin group were diagnosed as having *M. pneumoniae* infections (serologically). All of the patients were reported to have been clinical cures. Two patients were serologically diagnosed with *C. pneumoniae* in the gatifloxacin treated arm. All of the patients had a good clinical result. Two patients in the gatifloxacin treatment group were identified as being infected with *L. pneumophila*, based primarily on serologic diagnosis. These patients were considered clinical cures. While it is important to document clinical activity to all potential pathogens causing community acquired pneumonia, the diagnosis of atypical pneumonia remains problematic. It should not be stated that there was Microbiologic Eradication of these atypical pathogens, even though the definition in the protocol states that this could be based on clinical cure as a presumptive eradication. The FDA analysis reveals a smaller number of patients with documented atypical pathogens in this study. This study may support the inclusion of these pathogens in the label when taken in sum with the other CAP studies; however, it is highly recommended that a statement be made regarding the low numbers treated and the method of detecting the pathogen (serology).

The safety profile of gatifloxacin was similar to that of ceftriaxone at a dose of 1 to 2 grams per day. It appeared that gatifloxacin was tolerated slightly better than clarithromycin regarding the gastrointestinal side effects. Liver function abnormalities did occur in both treatment groups at a low level and to a mild degree, but this occurred more often in the ceftriaxone group. No significant clinical effects were a result of these changes. In addition, these changes may be, in part, due to the underlying pneumonia. The intravenous formulation appears to be well tolerated in comparison to the ceftriaxone group, with no major infusion site problems. No quinolone class adverse events were reported in this study: seizures, phototoxicity, tendon rupture, hypoglycemia, HUS or torsades de pointe. One case of torsades-de-pointe was reported to have occurred in the ceftriaxone treatment group.

## APPENDIX A

## Atypical Pathogen Serologic Data

\* indicates culture positive cases of *M. pneumoniae*

*Where serologic results are unchanged from the pre- value, only one value is listed.*  
*Where a pre- or post- test was not performed it is listed as ND.*

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3 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

### 8.1.3 STUDY # AI420-038A: Randomized, Double-Blind, Multicenter, Comparative Phase III Study of Gatifloxacin Versus Levofloxacin in the Treatment of Community-Acquired Pneumonia.

#### 8.1.3.1 STUDY DESIGN:

**OBJECTIVES:** To demonstrate efficacy of gatifloxacin (PO only, IV only or IV to PO) in the treatment of community acquired pneumonia and to compare the safety and efficacy of gatifloxacin 400 mg daily for 7 to 14 days to a standard regimen of levofloxacin 500 mg daily for 7 to 14 days, in the treatment of adults with community-acquired pneumonia.

**METHODOLOGY:** Randomized, double-blind, multicenter, prospective, comparative study.

*Medical Officer Comment: Note that a dynamic randomization method stratified by center was used in the conduct of this study. Please refer to Statistical Review for full discussion of this issue.*

#### CLINICAL PHASE: III.

**STUDY PERIOD:** 11/6/97 to 6/11/98

**INVESTIGATORS:** Multiple (61). Forty-eight Investigators enrolled patients.

**STUDY CENTERS:** 61 centers in the U.S. Patients were enrolled at 48 sites.

**PUBLICATIONS:** None.

**PROTOCOL AMENDMENTS:** There was one amendment to the protocol (prior to the enrollment of any patients), which applied to all Investigators. It clarified the inclusion/exclusion criteria; revised the pre-treatment studies to include additional tests for the detection of atypical pathogens; changed the nature of the post-study assessment; clarified the definition of Clinical Failure; corrected the concentration of gatifloxacin intravenous solution; clarified procedures to be done at the investigative site vs. the central laboratory; and allowed for optional collection of blood samples to assist in a pharmacokinetic/pharmacodynamic analysis.

*Medical Officer Comment: These amendments were a result of discussions held between the applicant and the FDA. While the applicant relied upon serology for the detection of atypical pathogens in the original protocol, FDA recommended culture be performed in order to document a portion of these infections microbiologically*

**8.1.3.1.1 DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Men and women, 18 years of age or older, newly hospitalized (<24 hours) or non-hospitalized, with clinical, laboratory, and radiologic findings suggestive of community-acquired pneumonia likely due to typical (e.g., *Streptococcus pneumoniae* or *Haemophilus influenzae*) or atypical (e.g., *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae*) pathogens.

Clinical evidence of pneumonia must have been demonstrated by a new infiltrate(s) on chest x-ray, and two or more of the following: fever ( $>38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$  taken orally,  $>38.5^{\circ}\text{C}$  or  $101.2^{\circ}\text{F}$  taken tympanically, or  $>39^{\circ}\text{C}$  or  $102.2^{\circ}\text{F}$  taken rectally); leukocytosis ( $>10,000\text{ WBC/mm}^3$  or  $>15\%$  bands); cough; chest pain; purulent sputum ( $>25\text{ PMN}$  and  $<10$  squamous epithelial cells per low power field); transtracheal aspirate, bronchial brushings, or biopsy material with Gram stain revealing neutrophils, and a predominant pathogen suspected by smear; direct lung aspirate with identification of a predominant pathogen on Gram stain; auscultatory findings such as rales or egophony.

Women of childbearing potential were required to have a negative pregnancy test within two days prior to the start of study medication and to agree to use an acceptable method of birth control throughout the study.

*Medical Officer Comment: Clinical resolution was based on those signs and symptoms listed above. Additional symptoms were collected, however; those listed above were considered to constitute the clinical endpoint definition for CAP.*

**8.1.3.1.2 NUMBER OF PATIENTS:** Enrollment: 418 patients; all but one levofloxacin patient received at least one dose of study drug (i.e., All Treated Patients 417). Two hundred and nine patients (107 female, 102 male) received gatifloxacin, 208 (123 female, 85 male) received levofloxacin.

**Demographics:** There were minimal differences between the two treatment groups with regard to age, race and weight. There was a higher proportion of females in the levofloxacin arm (59%) as compared to the gatifloxacin arm (51%). The vast majority of patients (84%) in both treatment arms were white.

*Medical Officer Comment: Almost two-thirds of all patients were enrolled at ten sites, with 94 (22%) enrolled at a single site (057). The remaining 38 sites enrolled ten or fewer patients each. It is of interest to note that two of the 11 sites with the highest enrollment had significant numbers of patients that were not clinically evaluable. However, when the statistical analysis controls for center, there is no influence on the outcome.*

#### **8.1.3.1.3 DISTRIBUTION OF PATIENTS:**

Clinically Eligible Patients: 203 gatifloxacin, 197 levofloxacin.

Clinically Evaluable Patients: 172 gatifloxacin, 178 levofloxacin.

Microbiologically Evaluable Patients: 92 gatifloxacin, 81 levofloxacin.

#### **Definitions:**

Clinically Eligible Patients: All Treated Patients with a diagnosis of community-acquired pneumonia at entry.

Clinically Evaluable Patients: All Clinically Eligible Patients who met the minimum dosing requirement of at least 5 days, (at least 3 days for treatment failures), had an end-of-treatment (in the case of failure) or post-treatment (Test of Cure) assessment in the interval Day +7 to Day +14, and did not receive a systemic antibacterial agent with documented activity against the causative pathogen between the time of the pre-treatment visit and the post-treatment assessment unless to treat a clinical failure.

Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had a bacterial pathogen susceptible to both study drugs isolated from a pre-treatment sputum and/or blood culture, or an atypical

pathogen diagnosed by culture, PCR, and/or serology; a sputum Gram stain performed for patients still producing sputum at the Test of Cure Visit, and a sputum culture performed for patients still producing sputum at the Test of Cure Visit if the sample was of good quality (i.e., >25 PMN and <10 epithelial cells/pf).

**Distribution of Patients in Subgroups and Reasons for Exclusion, All Treated Patients**  
**Protocol AI420-038**

Subgroup/Reason	Number of Patients (%)					
	Gatifloxacin		Levofloxacin		Total	
<b>Treated</b>	209	(100)	208	(100)	417	(100)
<b>Clinically Eligible</b>	203	(97)	197	(95)	400	(96)
<b>Clinically Ineligible</b>	6	(3)	11	(5)	17	(4)
<u>Reason Ineligible</u>						
No Evidence of Pneumonia on Pre-treatment X-ray	5	(83)	11	(92)	16	(94)
Other	1	(17)	-		1	(6)
<b>Clinically Evaluable</b>	172	(82)	178	(86)	350	(84)
<b>Clinically Unevaluable</b>	37	(18)	31	(15)	68	(16)
<u>Reason Clinically Unevaluable</u>						
Patient Clinically Ineligible	6	(16)	12	(39)	18	(26)
No Test of Cure Visit	14	(38)	8	(26)	22	(32)
Inadequate Dosing	11	(30)	6	(19)	17	(25)
Other	4	(11)	3	(10)	7	(10)
Other Systemic Antibiotic Given	1	(3)	2	(6)	3	(4)
One dose of Pre-treatment Antibiotic Received	1	(3)	-		1	(1)
<b>Microbiologically Evaluable</b>	92	(44)	81	(39)	173	(41)
<b>Microbiologically Unevaluable</b>	117	(56)	127	(61)	244	(59)
<u>Reason Microbiologically Unevaluable</u>						
No pre-treatment pathogen documented	102	(87)	116	(91)	218	(89)
Clinically Unevaluable	15	(13)	10	(8)	25	(10)
Pathogen Resistant to Study Drug	-		1	(1)	1	(<1)

(Reference vol. 6, p. 69)

**Medical Officer Comment:**

FDA review of reasons for Clinically Ineligibility via examination of the SAS transport data sets and CRF was generally in agreement with the applicant's table (see above).

One patient randomized to gatifloxacin never received study drug (#19-0115).

Clinically Unevaluability was also in agreement with the applicant's assignment. Of those patients designated as having the reason "other" one died early in the study, the others had CXRs performed very late in follow-up, or TOC visits at unevaluable time points outside of the specified windows.

Review of the reasons for Microbiologically Unevaluable via examination of the SAS transport data sets and CRF was generally in agreement with the applicant's table (see above).

In general, the two treatment groups were balanced with regard to number of patients excluded from various analysis cohorts. Four percent of patients randomized were ineligible, 16% were clinically unevaluable, and 59% were microbiologically unevaluable for analysis.

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBERS:**

Gatifloxacin 400 mg IV, Lot Number C97318; gatifloxacin tablets, 400 mg PO, Lot number N97078; matching placebo tablets, Lot number N97116. Tablets were supplied in blister cards.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**

Levofloxacin 500 mg IV, Lot number UL 4001, levofloxacin capsules, 250 mg PO, Lot numbers N98001, C97286; matching placebo capsules, Lot number N96129. Capsules were supplied in blister cards.

**8.1.3.1.4 DURATION OF TREATMENT:** Gatifloxacin QD (PO only, IV only or IV to PO) x 7 to 14 days; levofloxacin, QD (PO only, IV only or IV to PO) x 7 to 14 days.

The total number of days of therapy and number of doses was comparable between treatments groups. Eighty-eight percent of patients received oral therapy only, and five patients (1%) received IV therapy only (4 gatifloxacin; 1 levofloxacin). There was a wide range in the duration of therapy. The most common duration of dosing was 14 days, and was encountered in 195 (47%) patients. About 40% of patients received a 7 - 10 Day course of therapy.

Only 30 patients received less than seven days of therapy. The most common reasons for receiving less than seven days of therapy was discontinuation due to an adverse event or loss to follow-up.

All but two cases of an apparent extended duration of therapy in each treatment arm can be explained by skipped days during therapy or misrecorded dates on the CRF; one

patient in each treatment arm received one dose of IV study drug followed by 14 days of oral therapy for a total duration of 15 days (gatifloxacin 057-539; levofloxacin 019-113). One gatifloxacin patient received two doses of IV drug followed by 13 days of oral therapy for a total duration of 15 days (057-155). Finally, one levofloxacin patient (057-540) received 2 days of IV therapy followed by 14 days of oral therapy for a total duration of 16 days.

**Dosing Regimen and Study Medication,  
All Treated Patients  
Protocol A1420-038**

	Number of Patients (%)					
	Gatifloxacin N = 209		Levofloxacin N = 208		Total N = 417	
IV Only	4	(2)	1	(<1)	5	(1)
IV to PO	20	(10)	24	(12)	44	(11)
PO	185	(89)	183	(88)	368	(88)
<b>Total Duration (Days)</b>						
<5	18	(9)	10	(5)	28	(7)
5 - 6	-		2	(1)	2	(<1)
7	27	(13)	31	(15)	58	(14)
8 - 9	9	(4)	11	(5)	20	(5)
10	40	(19)	39	(19)	79	(19)
11 - 13	14	(7)	9	(4)	23	(6)
14	96	(46)	99	(48)	195	(47)
≥ 15	5	(2)	7	(3)	12	(3)

(Reference vol 6. P. 85)

Forty-nine (12%) patients received IV study medication, 24 gatifloxacin patients and 25 levofloxacin patients. Seventy-nine percent of those patients received only one or two doses of IV study medication before being switched to oral therapy. Twenty-five patients were hospitalized to receive IV study drug (14 gatifloxacin; 11 levofloxacin).

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**IV Study Medication Usage, All Treated Patients  
Protocol AI420-038**

	Number of Patients (%)					
	Gatifloxacin N = 209		Levofloxacin N = 208		Total N = 417	
Patients Receiving IV Therapy	24	(11)	25	(12)	49	(12)
<u>Number of IV doses</u>						
1	4	(17)	7	(28)	11	(22)
2	14	(58)	15	(60)	29	(59)
3	1	(4)	-		1	(2)
4	4	(17)	2	(8)	6	(12)
7	1	(4)	-		1	(2)
14	-		1	(4)	1	(2)
<u>Duration of IV (Days)</u>						
1	4	(17)	7	(28)	11	(22)
2	14	(58)	15	(60)	29	(59)
3	1	(4)	-		1	(2)
4	4	(17)	2	(8)	6	(12)
7	1	(4)	-		1	(2)
14	-		1	(4)	1	(2)

(Reference vol 6, P. 87)

*Medical Officer Comment: In general, the exposure to study therapy was similar between the two treatment groups. Roughly 12% of the study population was treated with IV only or IV to PO therapy, a relatively small percent.*

#### 8.1.3.1.5 CRITERIA FOR EVALUATION:

Efficacy analyses: Clinical and bacteriologic responses were determined from data at the Test of Cure Visit scheduled between Day +7 to Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit between Day +5 to Day +28 inclusive, was acceptable. Treatment Failures could be assessed at any time during the treatment and follow-up periods, but patients had to receive a minimum of three days' study drug therapy.

### Study Procedures Protocol AI420-038

Procedure	<u>Pre-treatment</u> (within 48 hrs prior to dosing)	<u>During</u> <u>Treatment</u> (Days 2 to 4) <sup>a</sup>	<u>End of</u> <u>Treatment</u> (Days +1 to +3) <sup>b</sup>	<u>Post-</u> <u>Treatment</u> (Days +7 to +14) <sup>a</sup>	<u>Final</u> <u>Follow-up</u> (Days +21 to +28) <sup>c</sup>
Informed Consent	X	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-
Medical History	X	-	-	-	-
Physical Exam	X	X <sup>d,e</sup>	-	X	X <sup>d,f</sup>
Vital Signs <sup>g</sup>	X	X <sup>e</sup>	-	X	-
Clinical Symptoms	X	X <sup>e</sup>	X	X	X
Clinical Signs	X	X <sup>e</sup>	-	X	X <sup>f</sup>
O <sub>2</sub> Saturation or ABG <sup>h</sup>	X	X <sup>i</sup>	-	-	-
Blood Cultures	X	X <sup>i,j</sup>	-	X <sup>i,j</sup>	X <sup>i,j</sup>
Respiratory Specimen Evaluation	X <sup>k</sup>	X <sup>k</sup>	-	X <sup>k</sup>	X <sup>k</sup>
Chest X-ray	X	X <sup>i</sup>	-	X	X <sup>f</sup>
Laboratory Tests	X	X <sup>l,m,n</sup>	-	X <sup>m</sup>	-
Serology Test	X <sup>o</sup>	-	-	X	X
Oropharyngeal Swabs <sup>p</sup>	X	-	-	-	-
Pregnancy Test	X	-	-	X	-
Assess Adverse Events	-	X	X	X	X
Assess Study Medication Use	-	X	X	X	-

<sup>a</sup> Patients discontinuing study prematurely will have post-treatment procedures performed prior to non-study antibiotic administration.

<sup>b</sup> Telephone contact. Immediate office visit and post-treatment procedures if the patient is not clinically improved.

<sup>c</sup> An office visit will be required during this time interval in all patients.

<sup>d</sup> Chest exam only.

<sup>e</sup> Repeat daily while hospitalized.

<sup>f</sup> If evidence of relapse.

<sup>g</sup> Blood pressure, pulse, respiratory rate, temperature.

<sup>h</sup> For hospitalized patients, oxygen saturation by pulse oximeter on room air or arterial blood gas on room air.

<sup>i</sup> If clinically indicated.

<sup>j</sup> If previous blood culture is positive.

<sup>k</sup> Macroscopic evaluation, Gram stain, culture/susceptibility testing if specimen obtained.

<sup>l</sup> Repeat every 3-5 days while hospitalized.

<sup>m</sup> Must be done. All abnormal laboratory test results should be repeated until they return to pre-treatment levels or are deemed clinically insignificant by the Investigator.

<sup>n</sup> Two blood samples (i.e., trough and peak) may be drawn for PK assessment on Day 2, in consenting patients who did not receive IV therapy.

<sup>o</sup> Including *Legionella* urinary antigen.

<sup>p</sup> Two swabs, one for PCR (*M. pneumoniae*, *C. pneumoniae*, *Legionella* sp.) and *M. pneumoniae* culture, and one for *C. pneumoniae* culture.

(Reference vol. 6, p. 38)

#### Medical Officer Comment:

*It is of interest to note that the applicant changed the test of cure window from +7 to +14 days to +5 to +28 days inclusive. This was done in an analysis plan submitted to the*